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Original Communications

WHOOPING COUGH

I. VACCINE AND SERUM PROTECTION EXPERIMENTS

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BAILLOU, in 1578, described a disease characterized by spasms of coughing. This condition is apparently the first description of whooping cough. Very few advances in the study of this disease were made until 1900 when Bordet discovered the causative microorganism of whooping cough in the sputum of his 5-month-old daughter. In 1906 Bordet and Gengou[1] successfully cultivated *H. pertussis* on an artificial medium. Chievitz and Meyer,[2] 1916, Madsen,[3] 1924, Lawson and Mueller,[4] 1927, Gardner and Leslie,[5] 1932, Sauer,[6] 1932, and Silverthorne and Fraser,[7] 1935, demonstrated that the "cough plate" is a reliable method for the isolation of the causative agent of whooping cough from patients. Wilcox[8] and Kristensen[9] were unable to demonstrate the carrier state in children with other diseases, in normal persons, or in those in contact with the disease. In 1935 Silverthorne and Fraser[7] demonstrated morphologic, cultural, and serologic differences between freshly isolated and stock strains. Such findings also were reported by Leslie and Gardner,[10] Coffey,[11] and Shibley and Hoelscher.[12] The experience of Toomey, McClelland, and Leider[13] and Shibley[14] showed that old strains had lost their pathogenicity. Silverthorne, Fraser, and Hendren[15] found that an old laboratory strain injected with mucin into mice does not produce death in these animals. Silverthorne[16] also demonstrated that a vaccine made from such a strain does not protect mice against an infection with freshly isolated strains suspended in mucin and injected intraperitoneally.

In a series of publications, Madsen,[17] Sauer,[18-22] Macdonald and Macdonald,[23] Park,[24] Kendrick and Eldering,[25] Daughtry-Denmark,[26] Kramer,[27] Howell,[28] Singer-Brooks,[29, 46] Miller and Faber,[30] Silverthorne, Fraser, and Brown,[31] Silverthorne, Fraser, and Hendren,[15] and Silverthorne[32] have reported results which suggest that children may be suc-

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cessfully immunized against whooping cough. Doull, Shibley, and McClelland,[33] Doull and associates,[45] and Siegel[34] were unsuccessful in demonstrating the value of this vaccine as an effective immunizing agent.

In recent years, studies on the production of experimental infection with *H. pertussis* in mice have been reported by Powell and Jamieson,[35] Burnet and Timmins,[36] Bradford,[37] Culotta and associates,[38] Ioffe and Hay,[39] Hornibrook and Ashburn,[40] and Lawson.[41] Silverthorne,[16] in 1938, demonstrated that a fatal septicemia may be produced in 90 to 100 per cent of mice when freshly isolated strains of *H. pertussis* suspended in mucin are injected intraperitoneally. This is true if a satisfactory batch of mucin properly suspended is made, if white Swiss mice free from disease are used, and if growth of culture and temperature conditions are uniform. If these requisites are met, satisfactory results may be obtained. Miller and Silverberg,[42] in 1939, confirmed the above results. This test serves a very useful purpose for evaluating the antigenic properties of vaccine and the protective effects of serum. Powell and Jamieson,[43] and Mishulow and co-workers[44] have shown that similar tests may be used in demonstrating protective antibodies in the serum of patients convalescent from whooping cough. Recently, Silverthorne, Cameron, and Walker have demonstrated protective antibodies in the serum of rabbits immunized with freshly isolated strains.[47]

From this brief review of the literature it is obvious that many contributions of importance have been made on methods of diagnosis on cultural and serologic differences in strains, on clinical studies of immunization, and on measurement of virulence and protection in animals.

INTRODUCTION

The present communication consists of further studies on the use of the mouse protection test in evaluating vaccines, on the minimal protective dose of vaccine in animals and on the blood serum of children examined before and after a course of fresh strain vaccine injections. The effect of normal and immune rabbit serum in the protection of mice infected with *H. pertussis* is reported.

OBSERVATIONS

One of us (N. S.)[16] reported preliminary results on the protective effect of fresh strain pertussis vaccines in mice. These studies have been extended and the same technique has been used. Each product was injected into ten mice, and in all experiments ten control mice of the same age were included. The lethal dose was found to be quite uniform (i.e., 90 to 100 per cent of control mice were killed in each experiment). The results are shown in Table I.

From Table I it may be seen that control mice, those vaccinated with pertussis antigens "L" and "G," those vaccinated with type B *H. influenzae* vaccine, and those which received vaccine made from an old

laboratory strain of pertussis subcultured for years on media devoid of fresh blood failed to survive and showed a fatality rate of 90 to 100 per cent. On the other hand, all vaccines made from fresh strain phase I *H. pertussis* protected 100 per cent of the animals with the following exceptions. One product, No. 10 in Table I, protected 90 per cent of the animals, and another product, No. 13 in Table I, protected only 60 per cent of the animals. Product No. 17 in Table I was a vaccine prepared from a strain of parapertussis kindly sent to us by Dr. Pearl Kendrick. It is to be noted that parapertussis vaccine (0.5 per cent phenol-killed) does not protect against the lethal dose of phase I pertussis strain used in these experiments. The dosage adhered to in vaccinating the mice with the various products listed in Table I was 0.25 c.c., 0.25 c.c.,

TABLE I

PROTECTIVE EFFECT OF PERTUSSIS VACCINES AND ANTIGENS

PRODUCT	FATALITY (%)	SURVIVAL (%)
1. Control (unvaccinated)	90-100	
2. *H. influenzae* type B vaccine	90-100	
3. *H. pertussis* antigen "L"	100	
4. *H. pertussis* antigen "G"	100	
5. Stock strain pertussis vaccine	100	
6. C—Fresh strain pertussis vaccine		100
7. P—Fresh strain pertussis vaccine		100
8. L—Fresh strain pertussis vaccine		100
9. O—Fresh strain pertussis vaccine		100
10. D.H.M. No. 59 pertussis vaccine		90
11. D.H.M. No. 61 (alum precipitated) pertussis vaccine		100
12. D.H.N.Y.C. pertussis vaccine		100
13. D.H.N.Y.S. pertussis vaccine		60
14. C—Fresh strain pertussis vaccine 1 mo. R.T.		100
15. C—Fresh strain pertussis vaccine 3 mo. R.T.		100
16. C—Fresh strain pertussis vaccine 6 mo. R.T.		100
17. Parapertussis vaccine (Kendrick)	80	
18. C—Fresh strain pertussis vaccine 0.5% phenol-killed		100
19. C—Fresh strain pertussis vaccine 0.2% formalin-killed		100
20. C—Fresh strain pertussis vaccine 1:5,000 merthiolate-killed		100
21. C—Fresh strain pertussis vaccine 1 hr. 56° C. heat-killed		100
22. C—Fresh strain pertussis vaccine 5% ether-killed		100
23. C—Fresh strain pertussis vaccine 0.5% phenol-killed*		100

*Culture grown in Hornibrook's fluid medium.
Letters refer to various commercial vaccines.

0.5 c.c., and 0.5 c.c. at intervals of five days with a two-week rest period and a final dose of 0.5 c.c. Two weeks following the last dose of vaccine the lethal dose of a strain of *H. pertussis* was injected.[16] Vaccines injected in these doses (whether they were killed by 0.5 per cent phenol, 0.2 per cent formalin, 1:5,000 merthiolate, heat of 56° C. for one-half an hour, or by 5 per cent ether) protected 100 per cent of animals. It is also noteworthy that products Nos. 14, 15, and 16 protected 100 per cent of the animals after the vaccine had been kept at room temperature for one, three, and six months respectively. We have shown (product No. 23) that a fresh strain pertussis vaccine grown on Hornibrook's medium protects 100 per cent of mice in this test.

The next problem was to assess the antigenicity of the vaccine by the injection of minimal doses into mice. In a previous publication[32] one of us (N. S.) reported results which, in preliminary experiments, indicated that undiluted fresh strain pertussis vaccine (0.5 per cent phenol-killed) protected mice after they had received 0.4 c.c., given in 0.1 c.c. amounts subcutaneously a week apart for 4 doses. Since that time additional experiments have been carried out on the minimal protective dose of pertussis vaccines in mice. The results are shown in Table II, and it is to be noted that there is slightly better, but perhaps not significant, protection with phenol-killed and boiled vaccine than with the other prepared vaccines.

TABLE II

MINIMAL PROTECTIVE DOSE OF VARIOUS PERTUSSIS VACCINES IN MICE
(Undiluted Product)

VACCINE KILLED BY	PROTECTION IN MICE WITH		
	0.3 c.c.	0.4 c.c.	0.5 c.c.
1. Phenol, 0.5%	+	+	+
2. Formalin, 0.2%	−	+	+
3. Merthiolate, 1:5,000	−	+	+
4. Ether, 5%	−	±	±
5. Heat, 1 hr. 56° C.	−	+	+
6. Heat, 1½ hr. 100° C.	+	+	+
7. Filtrate*	−	−	∓
8. Phenol, 0.5%†	+	+	+

*Seitz filtrate from Gates 2 density living culture, phase I *H. pertussis* suspension.
†Grown in Hornibrook's fluid medium.
+ = protection.
− = no protection.

In addition to the study of antigenic effects of vaccines and filtrates, serologic characteristics of the blood of vaccinated children were studied. Five children were given 8 c.c. of fresh strain pertussis vaccine (15,000 million microorganisms per cubic centimeter), and one child received 6 c.c., with inoculations of 1 c.c. in each arm at weekly intervals until the respective doses had been completed. Samples of blood for serum were obtained from each child before the inoculations and from one to two weeks after the inoculations had been completed. Agglutinins, precipitins, and bactericidal and mouse protecting antibodies were studied. The results of these experiments are as follows:

Agglutination.—Agglutinations were carried out in the usual way, except that a living culture antigen was used and the tubes placed in a water bath at 37° C. for two hours and overnight at refrigeration temperature. The serum from five out of the six children showed the presence of agglutinins for *H. pertussis.* One serum, E. H., did not show the presence of agglutinins.

Bactericidal Effect.—In order to determine if the serum of vaccinated children contained any bactericidal action on freshly isolated strains of *H. pertussis,* the following simple technique was used. Petri dishes

containing the Bordet medium were evenly spread with a culture of a freshly isolated strain of *H. pertussis*. Immediately two drops of serum obtained from the child before vaccination and two drops of serum obtained after vaccination were gently placed on the spread plate. The plates were then incubated for four days and the amount of inhibitory effect noted by measuring the area of "clearing" in the growth. Although inhibition of growth occurred, our results do not clearly show whether this was due to the effect of fresh serum or to the development of bactericidal substances.

Precipitin Tests.—Samples of serum obtained from six vaccinated children were set up in precipitin tests. The tests were done as follows:

Serum collected before and after vaccination was diluted with normal saline 1:2 and put in a series of small capillary tubes. An equal amount of an antigen (supernatant of a forty-eight-hour growth of a freshly isolated strain of *H. pertussis* from five slopes of Bordet medium suspended in 5 c.c. of normal saline) was stratified on the surface of the serum dilutions. The mixture was incubated in a water bath at 37° C. for one to two hours and kept at icebox temperature overnight, and readings were made the next morning. Using this technique no precipitins were observed in any sample of serum obtained before or after the children had been vaccinated.

Mouse Protection.—We have shown that rabbits immunized with freshly isolated strains of *H. pertussis* develop protective antibodies in their serum when the serum is injected intravenously into mice prior to infecting the mice with freshly isolated strains of *H. pertussis* suspended in mucin by intraperitoneal injection.

TECHNIQUE OF MOUSE PROTECTION TEST

Young white Swiss mice of uniform weight (20 to 22 Gm.) are used. The tail vein is submerged in a water bath at approximately 56° C. for a few seconds prior to the injection of the test serum. The serum to be tested is injected in 0.5 c.c. amounts intravenously into the tail vein of the mouse two to three hours prior to the injection of the infecting dose. Three mice are used for each of the serum dilutions. The infecting dose, which is given three hours later, is prepared as follows:

The growth from fifteen Bordet slopes of a freshly isolated strain of *H. pertussis* is suspended in normal saline and made up to a density, as measured on the Gates turbidimeter, of 0.7 cm. From this standard density a 1:10 dilution of the suspension is made in 5 per cent hog's gastric mucin.* One cubic centimeter of this 1:10 mucin dilution is injected into each mouse intraperitoneally. The results of experiments carried out are shown in Table III.

*Wilson Laboratories, Chicago, Ill., Lot 31900.

TABLE III

MOUSE PROTECTION TESTS

NAME	AGE (YR.)	SERUM DILUTION BEFORE VACCINATION			SERUM DILUTION AFTER VACCINATION			IMMUNE RABBIT SERUM DILUTION		
		1:2	1:5	1:10	1:2	1:5	1:10	1:20	1:50	1:100
J. H.	1	3/3*	3/3	3/3	3/0	3/1	3/2	3/1	3/1	3/1
M. L.	7	3/3	3/3	3/3	3/1	3/2	3/2	–	–	–
R. B.	1½	3/3	3/3	3/3	3/3	3/3	3/3			
D. B.	4	Not sufficient serum			3/3	3/3	3/3	3/0	3/1	3/0
V. G.	7	Not sufficient serum			3/2	3/3	3/3			
E. H.	2¾	3/3	3/3	3/3	3/3	3/3	3/3			

*3/3 = 3 mice injected and 3 died.

DISCUSSION OF PROTECTION EXPERIMENTS

It has been shown that the infecting dose given in mucin intraperitoneally is capable of killing approximately 90 to 100 per cent of control mice. It is obvious that this infecting dose is a very severe test of the protective power of any immune serum. From Table III it can be seen that, with the serum obtained from six children who had received pertussis vaccine, no sample that was tested showed mouse protection before vaccination, and two samples (J. H. and M. L.) showed mouse protection after vaccination. With two other samples of serum obtained after vaccination (R. B. and V. G.), some of the mice survived twelve to twenty-four hours longer than with a control serum. Thus, there was some evidence of mouse protecting antibodies in four of six samples of serum obtained from vaccinated children. Hyperimmune rabbit serum which was used as an added control in this test showed mouse protection

TABLE IV

MOUSE PROTECTION TEST

PERTUSSIS IMMUNE SERUM

SERUM	DILUTION	MICE INJECTED	MICE SURVIVED
Normal rabbit serum	1:2	26	4
	1:5	26	3
	1:10	29	1
	1:50	6	0
	1:100	6	0
Immune rabbit serum	1:2	27	22
	1:5	29	21
	1:10	38	24
	1:50	11	4
	1:100	11	5
Immune human serum (Philadelphia)	1:2	6	6
	1:5	6	5
	1:10	6	2
Human serum oral vaccination (Dr. Dow)	1:2	3	1
	1:5	3	0
	1:10	3	0

Infecting dose, 1 c.c. of a 1:10 dilution in 5 per cent hog's gastric mucin of living culture of *H. pertussis* from a Gates 0.7 cm. density.

in dilutions of 1:100. It is believed that such a test is valuable in estimating mouse protecting antibodies in human and animal sera.

Recently we have examined the protective effect in mice of normal rabbit serum, human immune serum,* immune rabbit serum and a human immune serum produced by oral ingestion of pertussis vaccine.† Table IV summarizes the results of our experiments. It is to be observed that immune rabbit serum and immune human serum show protection in mice against a fatal septicemia due to *H. pertussis*. The human serum produced as a result of the ingestion of pertussis vaccine and the normal rabbit serum in our hands showed little, if any, protection. Thirty-nine out of forty inoculated control mice (receiving the infecting dose intraperitoneally) died.

DISCUSSION

The tests on the vaccines reported give one some confidence in phase I products for use in humans. Small doses of phase I pertussis vaccine (0.3 c.c. and 0.4 c.c.) protect mice against a very large dose of the living culture injected with mucin. Although from the evidence presented it does not follow that such vaccines will immunize humans, it does offer laboratory evidence of the antigenicity of such products. The mouse test has served a very useful purpose for measuring protective antibodies in human and animal sera. In this sense it has given us a laboratory assay of immune rabbit serum which may be of use in the immediate prevention and treatment of whooping cough.

SUMMARY

A brief review of the literature dealing with various investigations on whooping cough has been made.

Pertussis vaccines prepared by different methods have been tested for their protective effect against a fatal septicemia in mice.

It has been shown that phenolized pertussis vaccine and boiled vaccine in small amounts (0.3 c.c.) protect mice against a fatal septicemia.

Agglutinins and mouse protecting antibodies have been demonstrated in the blood serum of children vaccinated with fresh strain pertussis vaccines. No prepicitins have been found, and bactericidal substances are questionably present.

A satisfactory mouse protection test has been developed for use in testing both the antigenicity of vaccines and the protective power of serum.

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*Supplied through the kindness of Dr. A. C. McGuinness, Philadelphia Serum Exchange, Philadelphia.

†Supplied through the kindness of Dr. Ruth Dow of Montreal.

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WHOOPING COUGH

II. Preliminary Report on the Use of Immune Rabbit Serum in Immediate Protection of Contacts Against Whooping Cough

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IN NOVEMBER, 1940, we reported[1] on the development of an immune rabbit serum which we believed might be effective in the immediate protection of children after contact with whooping cough. Preliminary studies on the use of this serum in the immediate prevention of whooping cough in children after contact were presented in an address to the Canadian Public Health Association in December, 1940, and an abstract of this address was published.[2] Since that time we have had a longer period of time to observe the outcome of a group of control and inoculated children. This communication is a progress report of the use of pertussis immune rabbit serum in prophylaxis after contact with whooping cough.

OBSERVATIONS

A group of children was studied at the Preventorium in Toronto, as well as a few in private practice. The children had been exposed to whooping cough which was proved bacteriologically. Forty-seven of the group were followed for this study. None had any history of a previous attack of whooping cough or of having been inoculated against this disease. Twenty-seven were infants between the ages of 2 and 22 months. The remainder were children from 2 to 14 years of age. Twenty-two of the children were followed as controls and did not receive serum. Twenty-five children received 5 to 10 c.c. of pertussis immune rabbit serum intramuscularly from one to two weeks after their first contact. Of the twenty-two control children, seven developed whooping cough, and in four of these seven cough plates were positive. In the remaining three it was not possible to take cough plates. Of the twenty-five children who received pertussis immune rabbit serum, only one child

Table I

Immune Rabbit Serum in Prevention of Whooping Cough

NO.	HISTORY OF WHOOPING COUGH	HISTORY OF PERTUSSIS VACCINE	IMMUNE SERUM	DAYS OF CONTACT	DEVELOPED WHOOPING COUGH	
					CLIN.	BACT.
22	0	0	0	7 to 14	7	4
25	0	0	5 to 10 c.c.	7 to 14	1	0

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developed whooping cough, but it was not possible to take a cough plate on this child. The results are summarized in Table I.

SUMMARY

A preliminary study on the use of immune rabbit serum in the prevention of whooping cough after immediate contact with the disease suggests that such a serum may be valuable in the prevention of this disease.

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WHOOPING COUGH

III. "Pertussis Toxic Material" and the Effects of Antigens in Animals

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Evans and Maitland (1937)[1] demonstrated that they could extract a potent "toxin" by physical means which produced a hemorrhagic necrosis in the skin of rabbits and, when given intravenously, killed guinea pigs. Evans[2] later demonstrated that this material produced antitoxin which neutralized the toxins of *H. pertussis*, *Br. bronchiseptica*, and *B. parapertussis*. In this communication we are presenting evidence that in the main confirms the work of Evans and Maitland. In addition we have compared the antigenic effect in animals of "pertussis toxic material" and "pertussis toxoid" with the antigenic effect of various preparations of the "whole microorganism."

Preparation of Toxin

Preparation of the pertussis toxic material was carried out, as described by Evans and Maitland,[1] by freezing and thawing a distilled water suspension of a forty-eight-hour growth of freshly isolated phase I strain of *H. pertussis* thirty times. The suspension was finally frozen and dried. The dried bacilli were then ground in an agate mortar for one-half hour. The ground material was resuspended in distilled water and centrifugalized for one hour. We used an angular centrifuge at a rate of 3,500 R.P.M. instead of 13,000 R.P.M. This procedure gave us a water-clear supernatant. The supernatant was then frozen, dried, and sealed under vacuum in pyrex tubes. When used for skin tests in rabbits or intracardial injection in guinea pigs, a weighed amount of this dried toxin was suspended in distilled water and 0.2 c.c. amounts of the toxin dilution were injected intracutaneously into rabbits and weighed amounts of toxin in distilled water were injected intracardially into guinea pigs.

Titration of "Pertussis Toxic Material" in Rabbits' Skin and Intravenous Inoculations of "Pertussis Toxic Material" in Guinea Pigs

Several rabbits were injected intracutaneously with 0.2 c.c. of the following dilutions of a number of preparations of the "toxic substance"; 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, 1:512, representing 0.1, 0.05, 0.025, 0.0125, 0.006, 0.003, 0.0015, 0.0007, 0.0003 mg. of "toxic material" respectively. Dermonecrosis occurred as far as the 1:64 dilu-

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tion of "toxic material"; i.e., with .003 mg. The lesions were quite typical of those described by Evans and Maitland. In eighteen to twenty-four hours a white indurated area was seen with a few petechiae and hemorrhagic areas in the central part. The lesion went on to a definite hemorrhagic necrosis and ended in a scab with ulceration at the end of some days (Fig. 1). In addition, a number of guinea pigs were injected intracardially with various amounts of "pertussis toxic material" obtained from different preparations. It was found that 0.5, 0.3, 0.2, and 0.1 mg. per 100 grams of guinea pig killed most animals in a few hours.

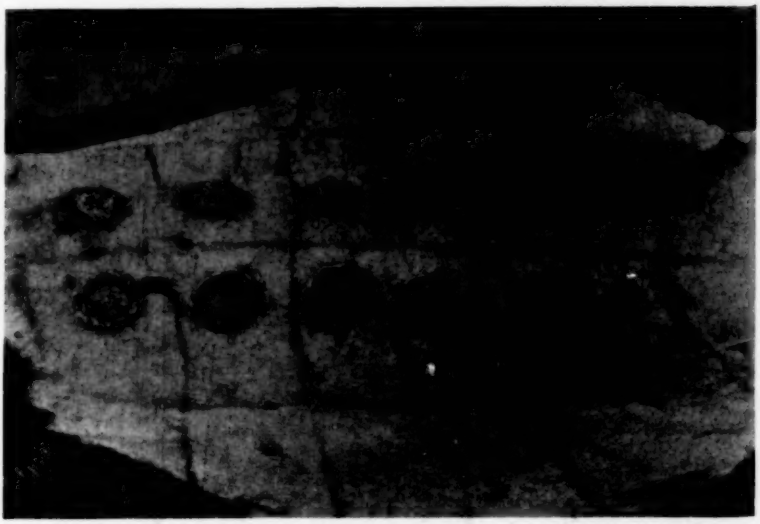

Fig. 1.—Dermonecrosis from various dilutions of "pertussis toxic material" in the skin of a rabbit. (Dilutions from left to right: 1:2, 1:4, 1:8, 1:16, 1:32, 1:64.)

TITRATION OF "PERTUSSIS TOXIC MATERIAL" WITH NORMAL AND IMMUNE RABBIT SERUM

Some time ago we produced[3] an immune pertussis rabbit serum of high agglutinating titer (1:10,000) and of high precipitin titer (1:10,000) which contained a mouse protecting antibody titer of 1:100 dilution of the serum. This serum was tested along with a control of normal rabbit serum in order to obtain information as to its ability to neutralize "pertussis toxic material." Equal amounts of the serum and "toxic material" were mixed and allowed to stand three hours at room temperature. An amount of 0.2 c.c. of the mixture of serum and "toxic material" of serial dilutions 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, 1:512 was then injected intracutaneously into rabbits, and readings were made in twenty-four, forty-eight, seventy-two, and ninety-six hours. On examining the reactions in the skin of the rabbits there was no evidence that the immune serum neutralized the "pertussis toxic material."

STUDIES ON THE NEUTRALIZATION OF "PERTUSSIS TOXIC MATERIAL" BY IMMUNE RABBIT SERA PREPARED BY INJECTING RABBITS INTRAMUSCULARLY WITH A NUMBER OF "PERTUSSIS ANTIGENS"

Experimental.—After rabbits had been bled to obtain samples of serum before the injections were given, each of three rabbits comprising a group were inoculated with pertussis antigens. The following pertussis antigens were injected into each group of three rabbits: (a) phase I living culture; (b) "pertussis toxic material" from phase I microorganisms; (c) "pertussis detoxified toxin" prepared according to method of Evans and Maitland[2]; (d) cell debris from phase I microorganisms washed free from toxin; (e) peritoneal washing of mucin suspensions of phase I living pertussis bacilli from mice dying as a result of this injection. Equivalent densities of Gates 2 cm. of the above-mentioned (a), (b), and (d) were used. A more concentrated form of (c), "detoxified toxin," and (e), the peritoneal mucin suspension of living *H. pertussis*, were used. The following doses of these antigens were given to the five groups: 0.6 c.c., 0.7 c.c., 0.8 c.c., 0.9 c.c., 1 c.c., 1 c.c. The interval was one week between inoculations, and a bleeding for testing of the serum from each group was done seventeen days after the last inoculation. Serum from each group of three rabbits was pooled and tested along with the control serum. The sera were tested for agglutinations, for toxin neutralizing antibodies, and for mouse protection.

Results.—All pooled sera from each group of the five groups of rabbits injected with the different antigens mentioned in the above paragraph showed the development of agglutinins to a phase I suspension of *H. pertussis*. Pooled sera from the group of three rabbits given (a) and (c) antigen (i.e., living culture phase I microorganisms and "detoxified toxin" respectively) neutralized the "pertussis toxic material." Pooled sera from the group of three rabbits given antigens (b), (d), (e) did not neutralize "pertussis toxic material." Mouse protection with the pooled sera from the groups of rabbits given antigens (a), (b), (c), (d), and (e) was done by a method previously described.[3] Pooled sera obtained from rabbits receiving (a), the living culture phase I *H. pertussis*, (b), the "pertussis toxin," and (d), the cell debris from phase I microorganisms washed free from toxin, showed some slight evidence of protection to a 1:10 dilution of the sera. Pooled sera obtained from rabbits receiving (c), the "detoxified toxin," and (e), the peritoneal washings from mice given mucin suspensions of living culture, showed no evidence of protection. The skin of rabbits which had been inoculated with antigens (a), (b), (c), (d), and (e) did not show any neutralizing power to "pertussis toxic material."

EFFECT OF INJECTING VARIOUS PERTUSSIS ANTIGENS INTO MICE

Experimental.—Young white Swiss mice (20 Gm. weight) were injected with (a) 0.5 per cent phenolized phase I pertussis vaccine, (b) "pertussis toxic material," (c) "pertussis detoxified toxic material," and (d) cell debris from *H. pertussis* washed free from "pertussis toxic material" and suspended in 0.5 per cent phenolized saline. Ten mice were injected with 0.1 c.c. at weekly intervals for four doses (a total of 0.4 c.c.) of each product. Each product represented material from the same density (i.e., Gates density of 2 cm.). One week after the last dose of each antigen, control mice and the four groups of mice which had received the antigens (a), (b), (c), and (d), were given the usual fatal dose intraperitoneally (i.e., 1 c.c. of 1:10 dilution in mucin) of living culture of *H. pertussis* from a Gates 0.7 cm. density as previously reported.[3] The results may be seen in Table I.

TABLE I

PROTECTIVE EFFECT OF "PERTUSSIS ANTIGENS" IN MICE

ANTIGEN	FATALITY (PER CENT)	SURVIVAL (PER CENT)
(a) Phase I pertussis vaccine (0.5 per cent phenol-killed)		90 to 100
(b) "Pertussis toxic material"		50
(c) "Pertussis detoxified toxic material"		90 to 100
(d) Cell debris phase I washed free of toxin (0.5 per cent phenol-killed)		90 to 100
Control mice	90 to 100	

DISCUSSION

From our experiments we have confirmed in the main the work of Evans and Maitland.[1] We have extracted a "toxic material" from phase I *H. pertussis* that causes a severe hemorrhagic necrosis in the skin of rabbits and that kills guinea pigs after intracardial injection. Titration of this material in the skin of rabbits revealed that a 1:64 dilution of the "toxic material" representing as small an amount as 0.003 mg. would cause necrosis with ulceration in the rabbit's skin. An immune rabbit serum which we have produced at the laboratory and which has been used in the prevention and treatment of whooping cough would not neutralize this "toxic substance" against the production of necrosis in rabbits' skin. This immune serum contained a high content of agglutinins, precipitins, and mouse protecting antibodies to phase I *H. pertussis*. In a group of rabbits inoculated with living culture phase I *H. pertussis* and "detoxified pertussis toxic material" (the latter from a more concentrated suspension of the toxic material than the living culture), sera were developed that did neutralize "pertussis toxic material" in the skin of normal rabbits. These sera also contained agglutinins. Mouse protecting antibodies in these sera were small in amount or absent. It is difficult to explain the results of these experi-

ments; namely, that a highly potent agglutinating and mouse protecting serum failed to neutralize "pertussis toxic material," whereas a moderately high agglutinating serum with a small amount or no mouse protecting antibodies did neutralize "pertussis toxic material" in the skin of normal rabbits. Although there are differences in the toxin neutralizing abilities of the groups of sera from rabbits injected with antigens (a), (b), (c), (d), and (e), it is noteworthy that from our experiments there is very little evidence that toxic extracts are any better than, if as good antigenically as, phase I strains of the whole microorganism. It is also to be observed in Table I that phase I (whole microorganism) phenol-killed vaccine, pertussis "detoxified toxic material," and cell debris washed free from "toxin material" protect mice against a fatal septicemia with *H. pertussis*. The mice injected with the "toxic material" were not protected as well as with the other antigens since only 50 per cent of the mice survived. Again, it is difficult to explain why mice immunized with "detoxified pertussis toxic material" were protected and mice injected with "toxic material" were not protected as well. It is quite obvious, however, from this experiment as with the former experiments, that the whole microorganism is equal, if not superior antigenically, to the "toxic material." From these experiments there is no laboratory evidence that "toxic materials" from *H. pertussis* are to be preferred to the whole microorganism in the development of products for the immunization of humans.

SUMMARY

Our experiments with "pertussis toxic material" confirm in the main the work of Evans and Maitland.

There is no laboratory evidence from our experiments in animals that "toxic materials" are preferable to vaccine made from the whole microorganism for use in human immunization.

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WHOOPING COUGH

IV. Beef Liver Extract Blood Agar Media for Growth of H. Pertussis

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ONE of the difficulties in the study of the growth of *H. pertussis* has been the fact that, until the discovery by Hornibrook of a semisynthetic fluid medium, this microorganism has been, for the most part, grown on the medium Bordet originated or some minor modification of it. Growth on Bordet medium depends on the addition of blood from 10 to 30 per cent. Although growth on Bordet medium occurs, it has not always been uniform and at times a strain shows marked retardation in growth or there is practically no growth. The reasons for such changes have not always been clear when conditions for growth are thought to be constant. Hornibrook[1] in 1939 developed a semisynthetic medium that supports the growth of phase I *H. pertussis*, and antigens made from the growth of *H. pertussis* in this medium, fulfil all the characteristics which we consider to be phase I. (See part I.) McLeod[2] obtained increased growth in beef liver extract with strains of streptococcus, staphylococcus, and pneumococcus. Using McLeod's technique of preparing the beef liver extract,[2] we experimented with it in the growth of *H. pertussis*. The purpose of our experiments was to see if beef liver extract either alone or with different amounts of added blood would support the growth of *H. pertussis*. We also wished to find out if reported subcultures of *H. pertussis* on this medium would keep the culture in its phase I state.

EXPERIMENTAL

A series of experiments were carried out to find out the ability of phase I *H. pertussis* to grow on beef liver extract agar with and without added citrated sheep's blood. In addition, we compared the growth of beef liver extract blood agar with that on Bordet medium. It was then necessary to find out if the strain of *H. pertussis* was maintained in its phase I state after repeated subculture. In other words, did the strain appear morphologically like phase I, did it agglutinate in high titer with phase I serum, did it kill mice when injected intraperitoneally with mucin, and finally did a vaccine made from growth after repeated subculture protect mice against a fatal septicemia, according to a method previously reported?[3]

RESULTS

Although some growth of *H. pertussis* occurred on beef liver extract agar without the addition of blood, it was found necessary to add sheep's

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blood to maintain subcultures. After several trials with additions of 1 c.c., 3 c.c. and 5 c.c. of citrated sheep's blood to 10 c.c. of beef liver extract agar, it was found that the best growth was obtained after the addition of 5 c.c. of citrated sheep's blood (33 per cent). The growth on this medium was much lighter in color and much more profuse, and the growth appeared earlier during incubation than on Bordet medium Fig. 1. After twenty subcultures at forty-eight- to seventy-two-hour intervals, the morphology appeared typical of phase I, and an antigen prepared from the growth in this medium agglutinated in high titer with phase I serum. In addition the intraperitoneal injection of a living culture suspension in mucin was fatal to mice. A vaccine prepared from the growth on this medium and killed in 0.5 per cent phenolized saline protected mice against an intraperitoneal injection of a living culture of Bordet-grown phase I strain suspended in mucin. In other words, beef liver extract blood agar preserves the phase I characteristics as we know them.

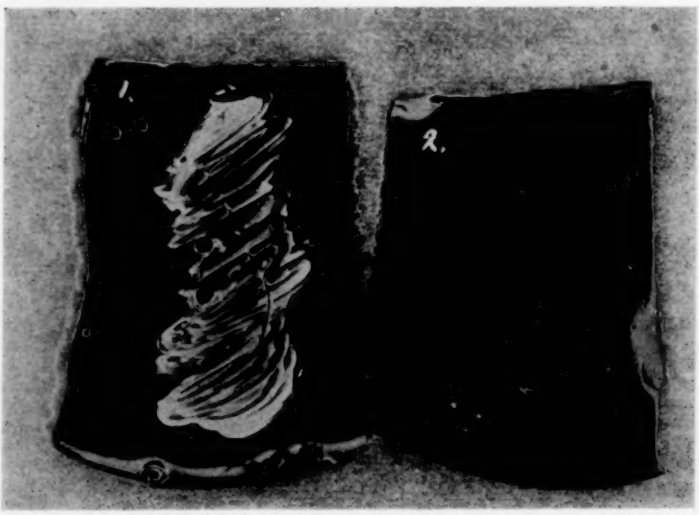

Fig. 1.—No. 1 shows growth of phase I *H. pertussis* on beef liver extract blood agar. No. 2 shows growth of phase I *H. pertussis* on Bordet blood agar.

SUMMARY

Beef liver extract agar with added citrated sheep's blood supports the growth of phase I pertussis.

After repeated subculture this medium preserves the phase I characteristics of *H. pertussis*.

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THE STIMULATION DOSE IN WHOOPING COUGH

JOSEPH H. LAPIN, M.D., BRONX, N. Y.

CRITICAL evaluation of immunization of children with phase I pertussis vaccines has now reached the stage where all workers agree that only studies based on intimate, sibling exposures can be used as criteria of the efficacy of immunization. The largest of these series show a percentage of failures ranging from Kendrick and Eldering's[1] 34.9 per cent and Miller and Faber's[2] 26.9 per cent to Singer-Brook's[3] 7.8 per cent. Since "a solid antibacterial immunity of duration comparable to artificially produced antitoxic immunities cannot be expected" (Miller and Faber), it would seem logical that the percentage of failures would increase with the time elapsed after immunization. In other words, from theoretical considerations, the percentage of failures in children immunized with vaccine should rise from year to year after the conclusion of immunization. However, the results of Miller and Faber[2] were quite the reverse. Calculating the communicability rate by six-month periods after the original immunization, they reported rates of 0 per cent, 57.1 per cent, 15.4 per cent and 20 per cent in successive periods. This failure of the communicability rate to rise with the time elapsed after immunization may be explainable by the small number of exposures (twenty-nine in thirty-four months), too few to be statistically conclusive.

In this study the purpose was to test the duration of immunity after whooping cough immunization, the effect of a "stimulating" dose of vaccine upon exposure, and the serologic effects of a "stimulating" dose of vaccine given to children immunized three to five years previously. In the clinical work, I am quite cognizant of the small number of exposures and that no conclusions of statistical significance may be drawn. However, the clinical work serves as an introduction to the study of the serologic effects of the "stimulating" dose.

I. THE DURATION OF IMMUNITY AFTER IMMUNIZATION

Of a group of 345 children who had received 80 billion of either Sauer vaccine or Mishulow's toxine vaccine, previously reported by the writer,[4] twenty-three recent exposures were analyzed. Table I shows the percentage of failures rising from 8.5 per cent two to three years after immunization to 57.1 per cent four to five years afterward. As mentioned, the number is of course too small to be significant.

From the Pediatric Service of the Bronx Hospital; Dr. B. S. Denzer, Director.

Thanks are due to Dr. W. A. Jamieson and Dr. H. M. Powell of the Lilly Research Laboratory who furnished the material and performed the serologic tests.

II. THE EFFECT OF A STIMULATING DOSE OF VACCINE GIVEN ON EXPOSURE UPON THE COMMUNICABILITY RATE

Twelve more of this original group of 345 children were seen shortly after intimate exposure to pertussis, usually to a sibling. Exposure had occurred from three to six years after the original immunization.

TABLE I

CHILDREN ORIGINALLY INJECTED WITH SAUER VACCINE INTIMATELY EXPOSED, WITH PERCENTAGE ACQUIRING THE DISEASE

TIME ELAPSED FROM IMMUNIZATION TO EXPOSURE (YR.)	TOTAL CASES	FAILURES	PERCENTAGE OF FAILURES
0-1	0	0	0.0
1-2	2	0	0.0
2-3	8	1	8.5
3-4	6	1	16.7
4-5	7	4	57.1
Total	23	6	26.1% average

TABLE II

CHILDREN ORIGINALLY INJECTED THREE TO SIX YEARS BEFORE WHO WERE INTIMATELY EXPOSED AND RECEIVED A STIMULATION DOSE OF 20 BILLION UPON EXPOSURE

TIME ELAPSED FROM IMMUNIZATION TO EXPOSURE (YR.)	TOTAL CASES	FAILURES	PERCENTAGE OF FAILURES
0-1	0	0	0.0
1-2	0	0	0.0
2-3	0	0	0.0
3-4	4	0	0.0
4-5	7	0	0.0
5-6	1	0	0.0
Total	12	0	0.0

All were given a dose of 20 billion of phase I, unwashed vaccine; all remained free of the disease. While small, this group nevertheless seems significant, especially by comparison with that shown in Table I. It must, however, be emphasized that the "stimulation dose" was given early in the exposure, since the parents of suspicious cases of whooping cough are constantly urged to refer contacts to the clinic immediately. Obviously, the exact day of exposure and the onset of the disease are difficult to determine in a disease like pertussis. However, in general, the stimulating dose was given to the contact after the sibling suspected of having pertussis had been coughing for from seven to ten days. Thus, stimulating doses were given to twice as many children as subsequent observation proved to have been exposed to pertussis. Only those cases have been studied in which the diagnosis of the suspected case of pertussis was later substantiated.

III. THE SEROLOGIC EFFECTS OF A STIMULATING DOSE OF VACCINE

This use of a "stimulation dose" in whooping cough is not new. Miller[5] and Shaw[6] suggested restimulation by injection at yearly inter-

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This use of a "stimulation dose" in whooping cough is not new. Miller[5] and Shaw[6] suggested restimulation by injection at yearly inter-

vals. MacLean[7] recommended an additional 4 billion on exposure or on entrance into school life. There are, however, no exact studies in the literature on the effect of a "stimulation dose" such as exist in diphtheria and tetanus. For this reason it was considered desirable to study the effect of a stimulating dose on a small group of those children included in the original mass immunization.

For this experiment, seventeen children were used. Ten cubic centimeters of blood were withdrawn for serologic tests. Nine children were given 10 billion, and 8 given 20 billion of pertussis vaccine (Lilly), and two weeks later, another 10 c.c. of blood were withdrawn for the follow-up serologic tests.

The criteria used for determining the efficacy of the "stimulating" dose are three: (1) the complement fixation reaction, (2) the rapid agglutination reaction, and (3), the intraperitoneal mouse protection test.

The complement fixation reaction was done by the method of Powell and Jamieson.[8] The author's[9] previous work with complement fixation reactions in children injected with 80 billion of vaccine had led him to expect a maximum response one week after the last dose and a return to negative by nine weeks after the last dose. An analysis of the results in Table III is therefore surprising in that of the 17 children immunized from three to five years previously, 8 still showed a 2+ to 4+ complement fixation test, even before the stimulation dose was given. The effect of the stimulation dose is evident in the reversal from a negative to a positive reaction in 3 children given 20 billion; anticomplementary reactions prevented the study of the effect of the stimulation dose in those children given 10 billion. The average for fifteen complement fixations before stimulation was 1.4+; the average for nine after stimulation was 3.0+.

RAPID AGGLUTINATION REACTION

The *rapid agglutination reaction* was done by a method to be published[10] in which the antigen is a formalinized suspension of *H. pertussis*, with 1.1 per cent sodium citrate, 1:10,000 merthiolate, and methylene blue, in a concentration of 100 to 120 billion organisms per cubic centimeter. A drop of this antigen is mixed with a drop of the patient's blood or serum on a glazed card; the card is tilted back and forth, and inspection is made for macroscopic agglutination after one minute, and after drying.

Comparison of the results after immunization and a stimulating dose has been possible in only a small series. Of 10 children who had received the customary 80 billion of Sauer vaccine, the agglutination test was 4+ in only 2, 3+ in 1, and 2+ in 7, when tested two weeks after the last dose had been given. Of 17 children tested three to five years after the original immunization, 9 still had a positive agglutination reaction (Table III). The effect on these 17 children of a stimulation dose of

10 to 20 billion is evident in an increase of agglutination in every case possible (i.e., if not 4+ before). The average of 17 agglutination tests before stimulation was 3.8+. The enhancement of a 3+ to a 4+ titer is not impressive. However, in 7 of the 17 cases, a negative agglutination test was raised by the stimulation dose to a 4+ reaction, a truly significant change.

The *intraperitoneal mouse protection test* was done by the method of Powell and Jamieson.[12] There are no references in the literature to this test performed three to five years after the original immunization. Mishulow, Klein, Liss, and Leifer[13] reported that of thirty-eight sera withdrawn from clinically typical cases of pertussis, thirty protected from 33⅓ to 100 per cent of the mice. It is interesting that the mouse protection tests (Tables III and IV) taken before the stimulation dose was given show that 13 of the 17 sera still showed significant mouse protection although from three to five years had elapsed since the original immunization. Mouse protection tests taken two weeks after stimulation give exactly the same results, thirteen out of seventeen sera positive. Mention has been made in a previous publication[14] of the fact that unaccountable variations in the virulence of *H. pertussis* may account for the paradoxical results, as in sera numbers 27 and 39, which showed a mouse protection titer before stimulation, and none afterward. The effect of a stimulation dose on the mouse protection titer is therefore difficult of evaluation.

Comparison of the effects of different dosages of vaccine given as a stimulating dose is shown in Table V.

TABLE V

COMPLEMENT FIXATION

	10 BILLION		20 BILLION	
	AVERAGE	REVERSAL − TO +	AVERAGE	REVERSAL − TO +
Before stimulation	1.2	--	1.4	--
After stimulation	*	*	2.9	4 of 8 cases
RAPID AGGLUTINATION				
Before stimulation	2.5	--	1.0	--
After stimulation	3.7	5 of 8 cases	3.9	3 of 9 cases
MOUSE PROTECTION TEST				
Before stimulation	--	--	--	--
After stimulation		1 of 9 cases		2 of 8 cases

*Of nine given 10 billion, seven were anticomplementary, so that no average could be drawn.

Complement fixation could not be used to evaluate the difference between 10 and 20 billion of the vaccine because of unfortunate anticomplementary phenomena in 7 of the 9 given 10 billion. The agglutination test shows a slightly greater rise in titer after 20 billion than after 10 billion. The mouse protection test shows no quantitative difference.

TABLE III

STIMULATION STUDY

SERUM NO.	INITIALS	AGE (YR.)	YEAR IMMUNIZED	HIST. EXPOSURE	STIMULATION DOSE (BILLIONS)	COMPLEMENT FIXATION		AGGLUTINATION		MOUSE PROTECTION	
						BEFORE STIM.	AFTER STIM.	BEFORE STIM.	AFTER STIM.	BEFORE STIM.	AFTER STIM.
1	P. C.	6	1937	1940	20	–	4+	–	4+	+	+
2	A. P.	7	1936	1940	20	–	4+	2+	4+	–	+
23	M. B.	6	1937	0	20	–	4+	3+	4+	+	+
24	L. S.	6	1936	1940	20	4+	3+	3+	4+	+	+
25	J. R.	6	1937	0	20	3+	4+	–	4+	–	+
26	J. P.	6	1936	1939	20	–	–	–	4+	+	–
27	V. K.	7	1937	0	20	3+	2	–	4+	+	+
38	A. D.	8	1938	0	20	–	2	–	3+	+	QNS
39	M. G.	8	1937	0	10	2+	Anticomp.	3+	4+	+	–
30	D. D.	6	1937	0	10	2+	Anticomp.	4+	4+	+	+
31	I. D.	9	1938	0	10	2+	Anticomp.	–	3+	+	+
32	P. B.	6	1937	0	10	3+	Anticomp.	3+	4+	+	–
37	M. F.	9	1938	1941	10	–	3+	–	3+	+	+
40	J. B.	5	1937	1940	10	–	Anticomp.	4+	3+	+	+
41	F. G.	5	1938	0	10	Anticomp.	Anticomp.	2+	4+	+	+
43	J. B.	4	1937	0	10	–	Anticomp.	4+	4+	–	+
44	F. A.	7	1937	0	10	2+	4+	–	4+	–	-

TABLE IV

MOUSE PROTECTION TESTS

IMMUNITY TEST DOSE OF PERTUSSIS CULTURE PER C.C.	CONTROL MICE (A)	CORD BLOOD PLACENTA	HUMAN IMMUNE BLOOD	RABBIT IMMUNE BLOOD	NO. 1, F. C.	NO. 2, A. F.	NO. 23, M. B.	NO. 24, L. S.	NO. 25, J. R.	NO. 26, J. P.	NO. 27, V. K.	NO. 30, D. D.	NO. 31, F. D.	NO. 32, F. B.	CONTROL MICE (B)	NO. 37, M. F.	NO. 38, A. D.	NO. 39, M. G.	NO. 40, J. B.	NO. 41, F. G.	NO. 43, J. B.	NO. 44, F. A.	CONTROL MICE (E)
10^{-1}	DDDDD	DD	DS	DS	DS		D	DS	DD						DD	DD						DD	
10^{-2}	DDDDS	DDSSS	SSSSS	SSSSS	SSS	D	SSSSS	DSSSS	DDDDS	DSS	SS	SS	SS	DS	DD	SS						DD	
10^{-3}	DSSSS	DS	SSS	SSS			SS	SS	SS			SS	SS	SS	DS	SS						DS	
10^{-4}	SSSSS	–	+++	+++	+		+	+	–	+	+	+	+	+	DS	+							
Result	*After Stimulation*																QNS	D	D	D	D	D	
	(C)														(D)	DD			DD	DD	DD	DD	(E)
10^{-1}	DD				DS	DD	DD	DS	DS	DD	DD	DD	DD	DD	DD	DD			DD	DD	DD	DD	DD
10^{-2}	DS				SS	DD	SS	SS	SS	DS	SS	DD	SS	DS	DD	SS			S	DS	DD	DD	DD
10^{-3}	SS				SS	SS	SS	SS	SS	SS	SS	SS	SS	DD	DS	SS			S	SS	S	D	SS
10^{-4}	SS	2A – Control		(D)	+	+	+	+	+	–	+	+	+	–	DS	+		+	+	+	+	–	SS
Result																							

D, Death of single mouse.
S, Survival of single mouse.

The series is evidently entirely too small to permit an evaluation of the effect of varying the dosages of the stimulation dose.

A comparison of the results of the complement fixation reaction, the rapid agglutination reaction, and the intraperitoneal mouse protection test shows a marked degree of correlation, although there are some unexplainable differences, such as a positive agglutination test, a negative complement fixation, and a positive mouse protection test becoming negative after stimulation.

DISCUSSION

The clinical work comprises, first, 23 exposures in 23 children who had been immunized with Sauer vaccine from one to five years before exposure, 6 of whom contracted whooping cough; and second, 12 exposures in 12 children who had been immunized with Sauer vaccine from three to six years before exposure and had received a "stimulating" dose of 20 billion vaccine as soon as possible after exposure, none of whom contracted the disease. The serologic work comprises rapid agglutination tests, complement fixation tests, and mouse protection tests on 17 children who had been immunized with Sauer vaccine from three to five years before a stimulation dose of 10 to 20 billion vaccine was given. Although small, the results of the series are sufficiently suggestive to warrant trying the same procedure on a large group. Should the results of such a study confirm my results, then definite recommendation can be made that a stimulating dose should be given on exposure. The duration of enhancement of immunity by a stimulating dose must also be studied before definite recommendations can be made. The optimum age at which to give a child a stimulating dose cannot be determined definitely now but will probably coincide with entrance into school.

SUMMARY

Twelve children, originally immunized three to five years previously, who received 20 billion of whooping cough vaccine upon intimate exposure to whooping cough, remained well.

A stimulation dose of 10 to 20 billion of whooping cough vaccine given to 17 children, originally immunized three to five years previously, resulted in:

(a) A change of the complement fixation reaction from negative to 4+ in 3 children, and an increase in the average complement from 1.4+ to 3.0+ two weeks after stimulation.

(b) An increase of the rapid agglutination reaction to 3+ or 4+ in all 17 children, and an increase in the average of 1.7+ before stimulation to 3.8+ two weeks after stimulation.

(c) A slight increase in the mouse protection titer. There was a slight advantage in giving 20 rather than 10 billion as the stimulating dose, but not enough in this small series to be statistically significant.

It is therefore tentatively recommended that all children receive a stimulation dose of 20 billion of whooping cough vaccine as soon as possible after exposure. Since it is as yet too early to judge the degree of permanence of the enhanced immunity afforded by the stimulation dose of whooping cough vaccine, it is only tentatively recommended that children receive a stimulation dose from two to five years after the original immunization.

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INFECTIOUS MONONUCLEOSIS: ITS TREATMENT WITH SCARLET FEVER CONVALESCENT SERUM

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IN 1889 Pfeiffer described a childhood illness associated with fever, swelling of the cervical lymph nodes, and an enlargement of the liver and spleen. The intervening years have gradually developed and clarified this clinical picture, now universally known as infectious mononucleosis. Although the clinical picture has been sufficiently defined as to establish the disease as an accepted clinical entity, so often does it simulate other conditions that recognition of the condition is far less frequent than its actual incidence. The majority of cases, especially in childhood, run such a mild and relatively short course that this frequent failure of recognition does not constitute a major medical problem. It also may be added that inasmuch as no successful treatment has been devised for the disease, its recognition has been more of academic than practical value. Furthermore, because the disease in both childhood and adult life frequently runs a short, mild course, this lack of specific medication usually is of little economic importance. A reduction of time loss from ten days to five or six days is of little moment to a young child. With increasing age this loss of time assumes a position of importance, often critical.

Moreover, all cases of the disease are not so mild or of such short duration as to be insignificant from the standpoint of morbidity. Although the incidence of the disease is fairly high in that age group to which time is of little value, the more severe forms and the greater incidence are in that age group where time often is of great value; namely, 12 to 40 years. The lack of specific therapy capable of shortening the course of the disease in this group constitutes a great handicap and makes for a marked economic loss of time.

At present the treatment of infectious mononucleosis consists mainly of those nonspecific measures usually employed in any acute febrile illness: bed rest, bland diet, and liberal fluid intake. Because of the markedly sore throat and the cervical adenitis invariably present, an ice collar is often used together with the usual gargles and topical applications. Aspirin is used with some benefit because of its analgesic and antipyretic action. In spite of all of these, however, the course of the disease remains unchanged, and recovery spontaneously occurs after a varying period of time, apparently quite unaffected by any treatment thus far employed. Because the marked membranous angina present in some cases so closely resembles the membrane of diphtheria as to be

mistaken for it, diphtheria antitoxin occasionally has been given before the true diagnosis has been established. As a matter of fact, some authors have reported benefit from the use of the antitoxin even in cases in which diphtheroids or nonvirulent diphtheria bacilli have not been found.[1] The reason for this is not quite clear inasmuch as bacteriologic studies have never shown any relationship between this disease and diphtheria. Moreover, such studies have never revealed so constantly the presence of any one organism as to lead one to believe that the agent causing the disease has been found.

When indefinite situations such as this occur, the tendency is to believe that the causative agent is a virus.[5] This situation prevails at present in infectious mononucleosis, many authors expressing the opinion that the disease is of virus origin. At present there is no factual data to support this point of view, and the etiologic agent, for the present, must be accepted as unknown. That the disease is of an infectious nature seems undoubted. Epidemics of some size have been reported[2] in both children and young adults. Multiple household infections also have been reported.[3] It must be admitted, however, either that the disease is not highly contagious or that for some reason a large proportion of the population is not susceptible. The latter is particularly evident in children under 2 years of age and in adults over 40 years of age. Predominantly involved is the age group of late childhood and young adult life.

When recently confronted with a severe case of the disease in the person of my own 20-year-old son, several forms of treatment were tried without avail. Local applications of 10 per cent silver nitrate to the ulcerated throat increased rather than diminished the discomfort. Adequate doses of sulfanilamide, likewise, had no appreciable effect.

The following case reports best indicate the course and the reasons for the use of scarlet fever convalescent serum which seemed so effective and constitutes the reason for this report.

CASE 1.—H. B., aged 20 years, bank clerk, a previously well young man with an irrelevant past history, except for a tonsillectomy at the age of 3½ years, began to complain of a sore throat on Aug. 27, 1940. The symptoms were not marked, and he continued to work during the next ten days. The temperature ranged from 99 to 100° F. Examination of the throat at the onset revealed redness and swelling of the pharyngeal lymphoid tissue and lingual tonsillar tags at the base of the tonsillar fossae. On the latter were several pinhead white spots of exudate. The cervical lymph nodes were both enlarged and tender.

Topical applications gave no relief. After several days the gingival margins appeared red and swollen. These were the cause of much discomfort and led to the impression that the infection was one of ulcerative stomatitis. For this, Talbot's solution (iodine, zinc iodide, glycerine, and water) was used with no apparent benefit. On September 7 the temperature had risen to 101°. The sore throat and the subjective symptoms of general malaise had increased to a point which demanded bed rest. The cervical lymph nodes were markedly enlarged and exquisitely tender. Constant use of an ice collar gave little relief, and the taking of food and fluids was

possible only by making use of the local analgesic effect of aspirin. Infectious mononucleosis had been thought of as a possibility, but a blood count on September 7 did not seem to confirm the suspicion: red blood cells 5,150,000; white blood cells, 6,925; neutrophiles, 59 per cent; lymphocytes, 33 per cent; monocytes, 6 per cent; and eosinophiles, 3 per cent. Increasing temperature, soreness of the throat, and cervical adenitis led to a repetition of the blood count on September 11: red blood cells, 5,245,000; white blood cells, 13,300; neutrophiles, 17 per cent; lymphocytes, 70 per cent; monocytes, 8 per cent; eosinophiles, 4 per cent; and basophiles, 1 per cent. The lymphocytes in this smear were typical of those found in infectious mononucleosis as described by Downey,[4] and the diagnosis was confirmed by Dr. Madeline Fallon, hematologist at the Children's Hospital, Los Angeles. The diagnosis was further confirmed by an heterophile agglutination test positive to the dilution of 1:1,280. The temperature gradually increased and ranged rather steadily between 101 and 102.8°. Swallowing, even of liquids, became almost impossible. The white spots on the tonsillar tags developed central areas of necrosis. Topical application of a 10 per cent solution of silver nitrate gave no relief or improvement. Sulfanilamide, given in adequate doses on the basis of a possible secondary streptococcic infection, gave no relief subjectively or in the temperature reaction. Because the symptoms constantly increased and the picture presented in the throat constantly simulated a severe streptococcic infection, it was decided to try scarlet fever convalescent serum. Using the same dose as would have been given a severe case of scarlet fever in a person of the same weight, 100 c.c. of scarlet fever convalescent serum was administered intravenously at noon on September 15. There were no immediate aftereffects, but by evening of the same day there was sufficient improvement to permit the eating of a small amount of food, the first in several days. On September 16 the temperature did not exceed 100°, and all foods were taken freely without discomfort. On and after September 17 the temperature was normal. The throat was not sore, the exudate disappeared from the tonsils, the cervical glands were markedly reduced in size and were not tender. Symptomatically, recovery was complete within a period of thirty-six hours. As a precautionary measure, bed rest was continued for several days. Work was resumed on September 23, but could have been resumed much earlier. On October 11 the blood count had returned to normal.

Having experienced this rather dramatic, rapid recovery, it became of great interest to try the serum again. The next case presented itself the following November.

CASE 2.—L. F., male, aged 20 years, university student, had an irrelevant past history. This illness began on Nov. 10, 1940, with a sore throat, and the patient was first seen by my associate, Dr. Fred L. Glascock. The picture presented appeared to be an acute attack of tonsillitis for which sulfanilamide in appropriate dosage was prescribed. Because of lack of improvement, he was seen again on Nov. 13, 1940. The throat at this time showed many small white ulcerated areas with some central gray sloughing. The cervical glands were markedly swollen and very tender. The voice was thick, and swallowing was difficult.

Because of the white spots in the throat, each presenting a central gray sloughing, infectious mononucleosis was suspected and a blood count taken. The blood count was: red blood cells, 5,145,000; white blood cells, 10,950; neutrophiles, 44 per cent; lymphocytes, 44 per cent; monocytes, 10 per cent; eosinophiles, 1 per cent; and basophiles, 1 per cent. The lymphocytes were typical of infectious mononucleosis. The following day the blood count was: red blood cells, 5,170,000; white blood cells, 13,750; neutrophiles, 25 per cent; lymphocytes, 63 per cent; monocytes, 10 per cent; eosinophiles, 1 per cent; and basophiles, 1 per cent. Blood obtained on November 14 for the heterophile test showed an agglutination in the dilution of 1:160.

The diagnosis of infectious mononucleosis having been definitely established, 100 c.c. of scarlet fever convalescent serum was administered intravenously at noon on Nov. 15, 1940. The following day he became afebrile; the subjective symptoms disappeared; and on the third day he returned to school quite recovered.

CASE 3.—A. R., aged 20 years, university student, was a patient for many years. This young man had a past history of no importance, except for a mild attack of poliomyelitis two years previously from which there had been a complete recovery.

He was first seen for this illness on Feb. 17, 1941. He complained of a stiff neck beginning the day previously, and when seen, presented only a mild cervical adenitis with a temperature of 101.5° F. He was placed on sulfanilamide in appropriate dosage. He was seen again on February 19 because of increasing sore throat and a temperature of 102°. The throat presented the typical picture of acute follicular tonsillitis, but because of the suspicion of infectious mononucleosis, a blood count was taken: red blood cells, 4,685,000; white blood cells, 10,950; neutrophiles, 49 per cent; lymphocytes, 41 per cent; monocytes, 9 per cent; eosinophiles, 1 per cent; and basophiles, 1 per cent. The lymphocytes were not considered typical of infectious mononucleosis at this time. During the following week he felt better and continued in school, but on March 3 he was seen again because of the return of the sore throat and a temperature of 101°. The findings were those of an ulcerative tonsillitis. The blood count was: red blood cells, 4,475,000; white blood cells, 18,675; neutrophiles, 21 per cent; lymphocytes, 64 per cent; monocytes, 12 per cent; eosinophiles, 2 per cent; and basophiles, 1 per cent. The diagnosis of infectious mononucleosis was made and confirmed by the blood smear by Dr. Fallon. The heterophile agglutination by the rapid method showed positive through a dilution of 1:640 and by the regular method through a dilution of 1:320.

At noon on March 4, 100 c.c. of scarlet fever convalescent serum was administered intravenously. That evening he telephoned that he felt "287 per cent better." The loss of the thick voice from tonsillar swelling was distinctly noticeable at this time. On March 5 the ulcerative areas were greatly reduced in size, and the tonsils and cervical glands were smaller. The highest temperature on this day was 100.5°. Subjectively he felt well and ate normally. On March 6 the temperature went to 99.1°. The ulcerated areas were gone from the left tonsil, and only one pea-sized area with raised edges remained on the right. The blood count was: white blood cells, 14,350; neutrophiles, 23 per cent; lymphocytes, 69 per cent; monocytes, 9 per cent; eosinophiles, 1 per cent; and basophiles, 1 per cent. He returned to school the following day.

CASE 4.—Having heard of our success in treating infectious mononucleosis with scarlet fever convalescent serum through Dr. C. M. Hyland, Director of the Serum Center, Dr. Gilbert J. Roberts of Pomona, Calif., treated a case similarly. His report by letter is as follows: "The patient, J. M., is a well-developed physically robust young male of twenty years, working in the Lockheed Assembly Plant. He was first seen by us on March 13, 1941, complaining of a sore throat and enlarged tender glands in the neck. Questioning revealed that he had not felt well for three weeks, since getting wet and chilled while working in the plant when it was flooded. At the onset he thought he had caught a severe cold or the flu, as he felt feverish and had a severe headache and general malaise. He laid off for a few days and then returned to work, but the headache persisted and about two weeks from the onset he consulted an optometrist because he thought the headache was due to eyestrain. The optometrist sent him to an osteopath who treated him for sinus trouble for a week without any benefit, and he developed a sore throat which has grown progressively worse the past week. This led him to consult us.

"On examination he appeared not acutely ill, but worn and listless. Temperature 100.4° F. Pulse, 90. The throat was very red, the tonsils moderately inflamed, and the anterior and posterior cervical glands and the posterior auricular glands enlarged and tender.

"Although no other glands appeared involved, infectious mononucleosis was suspected and the patient was hospitalized and a blood count made. This was sufficiently suggestive to warrant follow-up with a heterophile antibody test which was positive in 1:64 dilution. The patient showed no local improvement under ordinary treatment for pharyngitis and tonsillitis, continued to feel wretched, slept poorly, had night sweats and almost continuous headache for two days. [Author's Note: The temperature range for the period prior to the administration of the serum was 99 to 101.8°.] He was then given 100 c.c. of scarlet fever convalescent serum intravenously at 4 P.M. on March 15, fifty-two hours after hospitalization. There was almost immediate improvement. He did not have any further rise in temperature, slept well that night without sweating, and awoke in the morning without a headache and with a much more comfortable throat. The temperature subsided by lysis during the next thirty-six hours, and he continued to feel well. Glandular enlargement and tenderness rapidly subsided, and he was dismissed from the hospital on March 19.

"You may use any or all of this information as you please. It certainly looks as if you have discovered a prompt cure for a long-drawn-out troublesome disease."

DISCUSSION

It has been suggested that the disease we now term infectious mononucleosis may still need further clarification and that it may not actually be an entity but may be made of two or more closely related diseases. One series of cases associated with jaundice[6] and another with cerebral symptoms[7, 8] have been described in connection with the disease. At present, however, it seems safe to say that the disease is a clinical entity, but that it presents clinical pictures rather wide in variety. One obvious result of this variable picture is that many cases do and will continue to pass through medical hands either incorrectly diagnosed or not diagnosed at all. With increasing familiarity with the disease, more cases are certain to be recognized, and the need for an effective treatment will steadily become more apparent.

It seems inevitable that drugs of the sulfa group will be used in large numbers of these cases because of the prominence of the sore throat, the angina, and the cervical adenitis so commonly present. The use of sulfanilamide in this short series seems adequate to demonstrate its lack of value.

It is fully appreciated that four cases of infectious mononucleosis similarly treated and making similar rapid recoveries do not constitute unqualified proof that such treatment will always produce the same results. It is, however, most suggestive, and it is hoped that further experience will give results equally gratifying. It is possible that we have been fortunate in obtaining four cases of such similarity that they responded to the scarlet fever convalescent serum and that other cases presenting less adenitis, less angina, or more abdominal pain, jaundice,

or cerebral symptoms might not similarly respond. Future use of the serum should clarify this uncertainty.

Several points of speculative interest are brought out by this treatment:

1. Is infectious mononucleosis caused by one of the streptococcic group closely allied to the streptococcus of scarlet fever? For this question we have no answer, but the possibility seems to exist.

2. Is the benefit due to a nonspecific action of human serum? If this be true, similar results would be obtained by normal pooled human serum which we have not yet tried.

3. Is the 100 c.c. dosage the minimal, optimal, or maximal amount needed? The original dosage of 100 c.c. was selected because it was the amount a patient of the same age and body weight with scarlet fever would have been given. It is obvious that smaller doses should be tried, and this will be done as cases present themselves.

SUMMARY

Four cases of typical, proved infectious mononucleosis have been presented.

All patients were given 100 c.c. of scarlet fever convalescent serum intravenously.

All cases made complete clinical recoveries within forty-eight hours. No reactions and no relapses occurred in this small series.

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A COMPARISON OF ROUTINE URINALYSIS, ADDIS COUNT, AND BLOOD SEDIMENTATION RATE AS CRITERIA OF ACTIVITY IN ACUTE GLOMERULONEPHRITIS

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SINCE a small percentage of patients with acute glomerulonephritis are doomed to develop latent or chronic nephritis, it would seem important to recognize these individuals as early as possible and to single them out of the main body of acute nephritics who go on to early and complete recovery. The various criteria commonly employed in assessing complete recovery from an attack of acute nephritis are not entirely satisfactory. The most commonly used and simplest of the many tests, the routine urinalysis, obviously is no criterion of complete healing of the renal lesion, since the Addis sediment count reveals abnormalities long after careful routine urinalysis fails to show abnormalities. Certainly a "normal" renal function, estimated by any of the commonly employed renal function tests, does not preclude a continued activity of the disease, for often in the early stages when hematuria is still grossly present, the phenolsulphonephthalein excretion test or urea clearance test may be entirely normal and continue to be normal in the face of a persistent and prolonged hematuria. The sediment count of Addis is the most sensitive indicator of the continued activity of the disease. However, because of the technical difficulties involved, this test has not attained the widespread usage which it deserves. Certainly in outpatient and home practice with children the added possible inaccuracies of performance of the test make its use more difficult.

We have found that the blood sedimentation rate, a simple objective test, has given information concerning the prognosis and course of the patient with acute nephritis, not elicited by the routine urinalysis or renal function tests, but comparable to that obtained by repeated Addis counts. In many instances the blood sedimentation rate has given prognostic data not furnished by the Addis count.

The course of the acute glomerulonephritis attack was followed by means of the blood sedimentation rate in a group of forty patients admitted to the wards of the Children's Hospital of Philadelphia. These patients were kept in bed throughout their periods of observation. Simultaneously, Addis counts were made and blood sedimentation rates estimated at two-week intervals. Routine urinalyses were done more frequently, and periodic assessment of renal function by the urea clear-

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ance test and phenolsulphonephthalein excretion test were carried out. All patients were admitted to the hospital within five days of the onset of their disease.

Methods.—1. The blood sedimentation rates were done by the Cutler method, routinely employed in this hospital.[1]

2. The Addis counts were done according to the technique described by this author.[2, 2a] While we have counted all the formed elements in the sediment and have quantitated the protein in the twelve-hour urine specimens, we are reporting only the number of red cells in the sediment as an index of the trend of the Addis count. We feel justified in doing this because we have found that the red cells are the more constant and persistent abnormality. The value of 1,000,000 red cells per twelve hours has been taken as the upper limit of normality, since this was established in a previous study done in this hospital by Soto.[3]

Table I summarizes the average "recovery" times in days for each of the criteria employed in the group of forty patients followed to complete recovery by all the criteria used.

TABLE I

AVERAGE RECOVERY TIME IN FORTY CASES OF ACUTE GLOMERULONEPHRITIS

ROUTINE URINALYSIS	ADDIS SEDIMENT COUNT		SEDIMENTATION RATE (CUTLER)
	10 MILLION RED CELLS PER 12 HR.	ONE MILLION RED CELLS PER 12 HR.	
37 ± 18 days	76 ± 52 days	120 ± 75 days	86 ± 48 days.

From this data, it can be seen that while the routine urinalysis returned to normal on the thirty-seventh day, as an average, the Addis count required 120 days to achieve normality. There was a close correlation between the number of days it took for the twelve-hour red blood cell excretion (Addis count) to drop to the ten million level (seventy-six days) and the time required for the sedimentation rate to become normal (eighty-six days). For this latter reason this time has been included in Table I as an additional orientation point.

These data conclusively demonstrate the inadequacy of the routine urinalysis as a guide to the cessation of the active disease process.

The possible reasons for the return of the blood sedimentation rate to normal about thirty-four days earlier than the Addis count will be discussed below.

Table II illustrates the time sequences of the routine urinalysis, Addis count, and sedimentation rate in their return to normal in an individual case. It is interesting that on the fourteenth day, after admission to the hospital, when the routine urinalysis, Addis count, and sedimentation were all abnormal, the renal function of this patient (urea clearance) was already normal and remained so.

Tables III, IV, and V are illustrative of the effects produced upon the Addis count and sedimentation rate when infection supervenes

during recovery from acute glomerulonephritis. It is to be noted in Table III that there was a progressive fall in the sedimentation rate until the patient developed acute tonsillitis, at which time the sedimentation rate again became rapid. The fluctuations of red cell excretion at the higher levels noted in Table III are without significance, since daily Addis counts show great variability at these high levels in the early days of the disease. It required two months for the sedimentation rate to return again to its original level following the attack of acute tonsillitis.

TABLE II

CASE ILLUSTRATING COURSE OF ROUTINE URINALYSIS, ADDIS COUNT, AND SEDIMENTATION RATE IN AVERAGE PATIENT WITH ACUTE GLOMERULONEPHRITIS

DATE	NO. OF DAYS	ROUTINE URINALYSIS		ADDIS COUNT (MILLIONS OF RED CELLS PER 12 HR.)	SEDIMENTATION RATE (MM.—CUTLER)
		ALBUMIN	HEMATURIA		
7/19/40	0	++++	++++		32
8/ 2/40	14	0	+	49	27
8/16/40	28	0	+	66	18
8/21/40	33	0	+	36	14
8/29/40	41	0	+	33	14
10/ 1/40	74	0	0	15	7
10/23/40	96	0	0	17	5
11/15/40	119	0	0	10	7
12/20/40	154	0	0	1	6

TABLE III

INFLUENCE OF INTERCURRENT UPPER RESPIRATORY TRACT INFECTION ON SUBSIDING ACUTE GLOMERULONEPHRITIS

DATE	NO. OF DAYS	ADDIS COUNT (MILLIONS OF RED CELLS PER 12 HR.)	SEDIMENTATION RATE (MM.—CUTLER)
2/10/40	0		29
2/20/40	10	374	28
3/22/40	40	57	13
4/17/40	66	220	14
5/20/40	99	Acute Tonsillitis	
5/21/40	100	71	29
6/19/40	129	49	25
7/21/40	162	21	13
8/21/40	193	6.5	5
9/20/40	223	4.5	4
10/ 1/40	234	1.5	4

In Table IV the sedimentation rate which had become normal prior to the intervening infection was also accelerated for about ten weeks following the acute respiratory tract infection. In this patient, the exacerbations of the hematuria, by the upper respiratory tract infection, are shown by both the routine urinalysis and Addis count. This same sequence of events in another patient is depicted by Table V.

Table VI shows the effect of repeated intercurrent infections in a patient with glomerulonephritis. If the course of this patient's nephritis had been followed only by the routine urinalysis or the Addis count, it

TABLE IV

INFLUENCE OF INTERCURRENT UPPER RESPIRATORY TRACT INFECTION ON SUBSIDING ACUTE GLOMERULONEPHRITIS

DATE	ROUTINE URINALYSIS	ADDIS COUNT (MILLIONS OF RED CELLS PER 12 HR.)	SEDIMENTATION RATE (MM.—CUTLER)
11/17/39	++		30
11/27/39	±	48	29
12/21/39	0	9	15
1/26/40		11	9
2/15/40	UPPER RESPIRATORY TRACT INFECTION		
2/16/40	±	12	15
3/ 1/40	0	27	24
3/ 7/40	0	24	24
4/17/40	0	6	14
4/25/40	0	2	10

TABLE V

INFLUENCE OF INTERCURRENT UPPER RESPIRATORY TRACT INFECTION ON SUBSIDING ACUTE GLOMERULONEPHRITIS

DATE	ADDIS COUNT (MILLIONS OF RED CELLS PER 12 HR.)	SEDIMENTATION RATE (MM.—CUTLER)
11/30/38	48	29
12/ 7/38	35	24
12/21/38*	9	15
1/26/39	11	9
	UPPER RESPIRATORY TRACT INFECTION	
2/16/39	12	15
3/17/39	24	15
4/17/39	6	14
4/25/39	2	10

*Routine urinalysis normal in three weeks.

would appear that she had suffered four distinct attacks of nephritis during the period of eighteen months. However, this is highly improbable, for in an eight-year experience at this clinic, there has not been a single recurrence of acute glomerulonephritis in any patient who showed complete recovery (by Addis count and sedimentation rate) following the first attack. This permanency of recovery from acute glomerulonephritis in childhood has been noted by others.[4] Accordingly, the reappearances of hematuria must represent exacerbation of the original attack of nephritis. That the sedimentation rate remained accelerated throughout the entire eighteen-month period, even when the Addis count was normal, is highly significant and we believe is evidence that the nephritic process was still active despite the fact that excretion of red cells in abnormal numbers was absent. This is an instance in which the sedimentation rate would seem to furnish more information regarding the subsidence of renal "activity" than the Addis count. Examination of this patient two years later (1941) lends weight to this belief in that she now has evidence of chronic nephritis (persistent hematuria and rapid sedimentation rate). Moreover, in the patient with well-advanced chronic nephritis, there are periods during which the hematu-

ria even when measured by the Addis count is minimal; nevertheless, in these same patients the sedimentation rate is always rapid. Thus we feel that a persistently rapid sedimentation rate in a patient with acute glomerulonephritis, which cannot be accounted for by other infection, is indicative of persistence of the nephritis even though all other findings pertaining to the kidneys are apparently normal.

TABLE VI

INFLUENCE OF REPEATED RESPIRATORY TRACT INFECTIONS ON SEDIMENTATION RATE AND ADDIS COUNT IN GLOMERULONEPHRITIS

DATE	RENAL FUNCTION		ROUTINE URINALYSIS		SEDIMENTATION RATE (MM.—CUTLER)	ADDIS COUNT (MILLIONS OF RED CELLS PER 12 HR.)
	UREA CLEARANCE	P. S. P. EXCRETION (15 MIN.)	ALBUMIN	HEMATURIA		
11/ 7/37	55%		+++	+++		
12/ 1/37			0	+	29	
12/22/37			0	0	30	55.0
1/25/38			0	0	25	13.0
2/ 9/38			0	0	23	24.0
3/22/38			0	0	22	2.5
4/ 5/38	ACUTE TONSILLITIS (HEMOLYTIC STREP.)					
4/ 5/38			++	+	29	86.0
5/ 3/38			0	0	20	24.0
5/31/38			0	0	17	8.7
6/ 8/38			0	0	20	1.5
7/ 2/38	135%		0	0	23	0.2
	SECOND HOSPITAL ADMISSION—ACUTE TONSILLITIS					
10/22/38			++	++	23	
10/26/38			+	0	27	
11/ 1/38	175%	45%	0	0		17.0
11/19/38			0	0	24	1.1
2/15/39			0	0		0.4
	THIRD HOSPITAL ADMISSION—PNEUMONIA					
5/17/39			+++	+++	28	
5/29/39	95%	36+	+	±	31	37.0
6/ 8/39			+	±	31	50.0
6/22/39			+	0	29	44.0

Table VII depicts the course of a patient with what may be termed subacute glomerulonephritis as gauged by the Addis count. The return of the sedimentation rate to normal five months before the Addis count became normal was of extreme interest. In view of the fact that we had not encountered any previous patient with persistently normal sedimentation rates who did not go on to complete recovery, we felt justified in predicting, several months before the Addis count became normal, that it would ultimately become normal. This particular patient, in whom the sedimentation rate was so valuable a prognostic guide long before the urinary sediment became normal, is typical of the average behavior of the entire group of acute nephritics studied, as pointed out in Table I. The slight acceleration of the sedimentation rate and the increase in the sediment count following mumps is in our experience typical of the response of the convalescent nephritic to this and other contagious diseases.

TABLE VII

COURSE OF ADDIS COUNTS AND SEDIMENTATION RATES IN PATIENT WITH SUBACUTE GLOMERULONEPHRITIS

DATE	RENAL FUNCTION		ROUTINE URINALYSIS (HEMATURIA)	SEDIMENTATION RATE (MM.—CUTLER)	ADDIS COUNT (MILLIONS OF RED CELLS PER 12 HR.)
	UREA CLEARANCE	P. S. P. EXCRETION (15 MIN.)			
7/21/40	29%		++++	26	
8/15/40	70%	37%	++	23	577
9/13/40			+	21	64
10/ 1/40			0	16	52
10/23/40			0	14	33
11/27/40	118%		0	11	22
1/28/41			0	18 (Mumps)	8
2/14/41			0	12	16
3/ 5/41			0	9	10
4/16/41			0	6	2
5/14/41			0	6	1

TABLE VIII

ADDIS COUNT AND SEDIMENTATION RATE IN CHRONIC GLOMERULONEPHRITIS

PATIENT	DATE	ROUTINE URINALYSIS (HEMATURIA)	ADDIS COUNT (MILLIONS OF RED CELLS PER 12 HR.)	SEDIMENTATION RATE (MM.—CUTLER)
I. H.	10/12/39	++++		32
Urea clearance = 42%	11/20/39	+	4,500	32
B.U.N. = 55 mg. %	12/ 7/39	+	3,000	32
	12/13/39	++	1,500	32
	1/ 3/39	+	200	32
T. L.	5/29/41	+	9.4	21
Initial course in Table VI	6/17/41	+	2	19
C. Y.	8/ 5/37	++++		32
Urea clearance = 14%	8/18/37	++++		35
B.U.N. = 72 mg. %	9/ 2/37	++++	8	36
	9/15/37	++++		35
E. D.	4/12/39	++++		
Urea clearance = 10%	4/17/39	++++	88	31
B.U.N. = 240 mg. %	5/18/39	+	37	36
H. W.	7/22/40	++++		24
Urea clearance = 74%	8/13/40	+++		18
B.U.N. = 15 mg. %	10/ 1/40	++	14	21
T. M.	11/ 6/40	++	44	22
Urea clearance = 35%	12/ 4/40	+	53	18
B.U.N. = 38 mg. %	12/31/40	+	76	31
	1/15/41	±	87	27
	2/ 5/41		23	34
	2/12/41		97	31
	2/19/41	+	17	28
	3/19/41	++	19	26
	4/16/41	++	39	23
	5/15/41	+++	38	16
	6/18/41	+++	7	23
	8/13/41	+	14	19

Table VIII summarizes the data concerning the sedimentation rate in patients with chronic nephritis. Five of these patients were admitted to the hospital with well-established chronic nephritis. T. L., whose initial course was presented in Table VI, is the only patient we have encountered in 150 with acute nephritis who has developed chronic nephritis following an acute attack observed by us. In every instance regardless of the fluctuations of red cells and protein excretion the sedimentation rate remained rapid. At no time in any of these patients was the blood sedimentation rate normal in spite of the fact that extrarenal focal infection was not demonstrable over long periods of time.

There were three patients in whom the sedimentation rates became normal very rapidly and while there was still considerable hematuria. Table IX is typical of this small group. One is tempted to point out the analogy of this finding to the behavior of the sedimentation rate in certain acute rheumatic patients. While in the majority of acute rheumatic patients there is a close parallelism between the activity of the disease and the sedimentation rate, in an occasional case the sedimentation rate returns rapidly to normal while the rheumatic process is obviously active. Thus we feel that although these three patients, like the occasional rheumatic patient, did not conform to the usual pattern of behavior of the sedimentation rate, in no way do they negate the value of this test as a prognostic guide in the nephritic patient.

TABLE IX

RETURN OF SEDIMENTATION RATE TO NORMAL LONG BEFORE THE ADDIS COUNT BECAME NORMAL IN PATIENT WITH GLOMERULONEPHRITIS

DATE	ROUTINE URINALYSIS (HEMATURIA)	ADDIS COUNT (MILLIONS OF RED CELLS PER 12 HR.)	SEDIMENTATION RATE (MM.—CUTLER)
12/ 5/37	++++		34
12/27/37	++	123.0	27
1/26/38	0	100.0	10
2/23/38	0	29.0	7
3/ 9/38	0	25.0	7
3/22/38	0	75.0	7
3/29/38	0	33.0	5
4/15/38	0	19.5	6
5/ 3/38	0	7.0	
8/ 5/38	0	3.9	
2/16/39	0	0.0	

DISCUSSION

Since infection, usually of the upper respiratory tract, precedes the attack of acute glomerulonephritis, and since this type of infection accelerates the sedimentation rate, one might justly question whether the rapid sedimentation rate is entirely dependent upon the antecedent infection and whether the renal disturbance has any part in its alteration. In the uncomplicated upper respiratory tract infection, such as usually occurred in our patients, the resultant rapid sedimentation rate

returns to normal in about three weeks; occasionally it is prolonged to five weeks.[5] In contrast to this it took twelve weeks, on the average, before the sedimentation rate was normal in the nephritic child, with an occasional case going beyond twenty-five weeks. Thus we feel that the antecedent upper respiratory tract infection cannot account wholly for the persistence of the rapid sedimentation rate and that the kidney disturbance must be responsible at least for the prolongation of the accelerated sedimentation rate. Furthermore the persistence of a rapid sedimentation rate in the absence of any detectable foci of infection in our patients with chronic glomerulonephritis argues that nephritis may be a responsible agent for the fast sedimentation rate in these patients. This is in keeping with the observation of Walton,[6] who found that there was a further increase in the sedimentation rate of the patient recovering from scarlet fever with the onset of acute glomerulonephritis.

If the return to normal of the sedimentation rate is a criterion of recovery from nephritis, why then does its return to normal precede the disappearance of abnormal numbers of red cells from the urinary sediment as was noted in Table I? All the factors governing the alteration in sedimentation rate are not elucidated, but it is believed that increase in globulin and fibrinogen are factors increasing the velocity of sedimentation. In acute nephritis, both from data published in the literature[7] and unpublished data of our own, there is evidence that the fibrinogen and globulin are elevated and that they return to normal with recovery from the disease. Thus the altered sedimentation rate in nephritis may be dependent upon such humoral factors of the disease and not upon anatomic changes in the kidney glomeruli. It is understandable then that in the process of recovery these altered humoral factors may achieve normality before complete anatomic healing of the glomerulus, thus resulting in the return of the sedimentation rate to normal values prior to the disappearance of the hematuria.

SUMMARY

There is a close correlation between the return of the sedimentation rate to normal and recovery from acute glomerulonephritis.

There is a correlation between the return of the sedimentation rate and the Addis count, the Addis count becoming normal about five weeks after the sedimentation rate. In those instances where there has been great disparity between the return of the sedimentation rate and the Addis count to normal, the sedimentation rate has been an equally if not a more reliable prognostic index than has the Addis count. However, of even greater prognostic significance is the return of both the Addis count and sedimentation rate to persistently normal levels for a period of several weeks.

Finally, the simplicity of the blood sedimentation test, which seems to be a valuable guide of the course of acute glomerulonephritis, recommends its use in this disease.

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NEW CONCEPTS OF GONOCOCCAL VAGINITIS

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RECENT advances in diagnosis and treatment have resulted in new concepts of gonococcal vaginitis as a pediatric problem which have not yet been generally accepted and applied by hospitals, child-caring institutions, schools, and other agencies which are chiefly concerned. For this reason it seems of value to present the conclusions of a study of gonococcal vaginitis which has been made for the past three years in various hospitals, clinics and child-caring institutions in New York City.

PREVALENCE

Gonococcal vaginitis was found to be less prevalent than had been estimated either from reported cases in the Department of Health records, or from the literature, or from the general impression among pediatricians and practicing physicians.[1, 2, 3, 4] During the period of this study there was no report of an epidemic of gonococcal vaginitis in any institution in New York City.

Since this study was primarily concerned with gonococcal vaginitis, it is impossible to say what proportion of all vaginal infections are due to the gonococcus, but it was ascertained that a large percentage of patients who were suspected of having a specific infection were found to be negative on bacteriologic examination. Of 1,715 patients who were studied because they had symptoms or were contacts of infected persons, only 381 (22.2 per cent) girls were positive.

DIAGNOSIS

Improved diagnostic measures are in large part responsible for a truer concept of the prevalence of this infection.[5, 6] The culture method[7] has proved to be superior to smears for diagnosis. It provides definite identification of the organisms so that false positive reports are avoided. Further, cultures are more accurate than smears, as the duration of the

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disease increases after treatment has been instituted. This is especially true for children receiving estrogenic therapy, when it may be difficult to identify the organisms in smears.

Fig. 1 shows the superiority of cultures over smears.

The cases reported were studied by smear and culture, both made at each observation. No patient was considered positive unless she had at least one positive culture, and no patient was considered cured unless there were at least seven consecutive negative smears and cultures during a period of at least sixteen weeks.

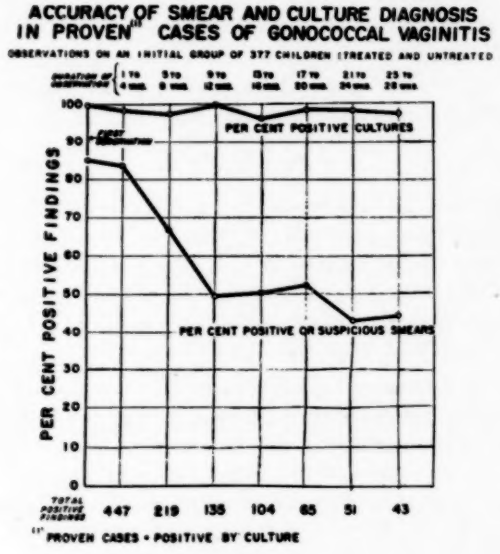

Fig. 1.

The method of obtaining specimens for smear and culture has been described.[6, 8] An ordinary glass female catheter containing normal saline is introduced into the vagina. On removal the discharge suspended in the saline is first used to inoculate broth for culture and then spread on glass slides for smear examination. The advantages of this method are that specimens are obtained painlessly from deep in the vagina without causing trauma and that one manipulation supplies material for both smear and culture so that results are more comparable than when separate swabs are used.

COURSE OF THE UNTREATED DISEASE

In order to evaluate properly various forms of treatment, forty-one children chosen at random and given no treatment of any sort were used as controls (Fig. 2). These included both ward and clinic patients.

Observation of this group gave a new concept of the natural course of gonococcal infection in girls. It became apparent that the disease in untreated patients underwent what was called "spontaneous cure."[9] Eighty-seven per cent of these children became and remained negative by all tests within twenty-eight weeks of observation. The period of observation, after spontaneous cure, averaged 45.9 weeks, and the average number of negative smears and cultures was 14.4. There was no recurrence of the infection among these children.

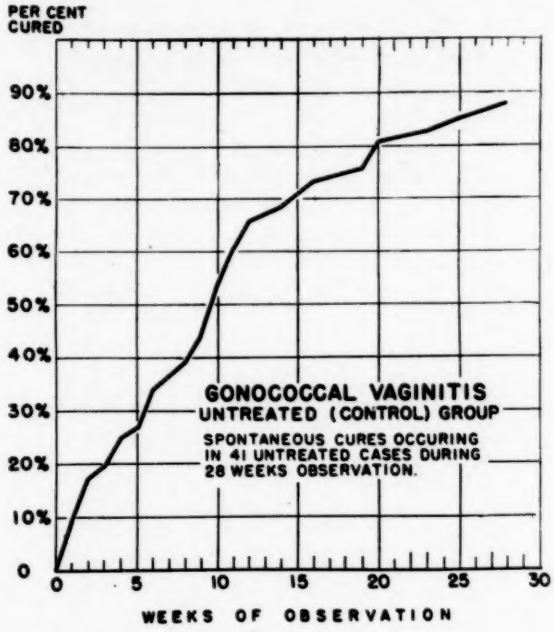

Fig. 2.

It is suspected that the chronicity and long duration of the disease which were observed previously possibly were a result of the older forms of therapy. The strong antiseptics and vigorous local treatment used probably delayed the healing processes of the tissues.

Clinically there was considerable variation in the course of the disease. The discharge may disappear early or it may persist for some time. However, by the end of the eighth week all gross discharge and signs of inflammation had usually disappeared. Some children who had no external discharge still had positive cultures. The presence of pus cells in the vaginal secretion was of little significance except during the acute stage of the infection. Children who had repeatedly negative smears and cultures showed many leucocytes in the vaginal smear. This was

similarly true in normal children. In a group of 1,284 normal, uninfected children examined routinely for admission to a children's shelter, 33 per cent of the cases showed many leucocytes in the smears (Fig. 3).[10]

In some children positive cultures were obtained at irregular intervals although there was never any vaginal discharge and smears were always negative. These were considered as "carriers." Such a child would not be suspected of harboring the gonococcus if only smears were used for diagnosis. These "carriers" ultimately became negative after prolonged observation without treatment.

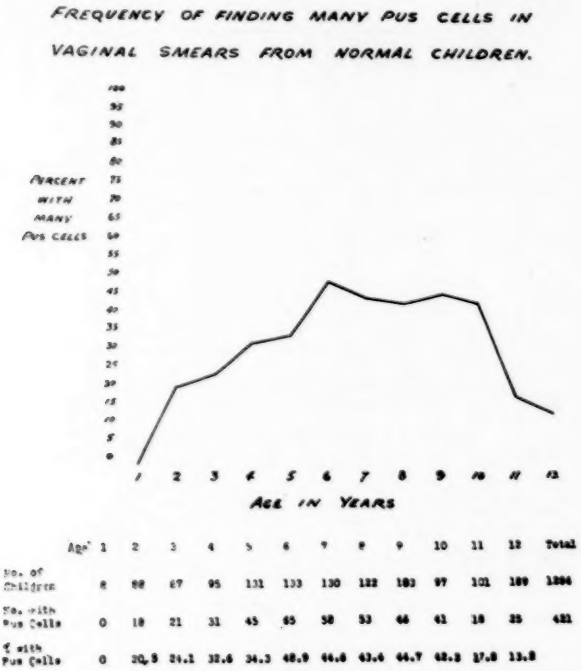
FREQUENCY OF FINDING MANY PUS CELLS IN VAGINAL SMEARS FROM NORMAL CHILDREN.
PERCENT WITH MANY PUS CELLS
AGE IN YEARS
Age 1 2 3 4 5 6 7 8 9 10 11 12 Total
No. of Children 0 88 67 95 131 133 130 122 103 97 101 109 1284
No. with Pus Cells 0 18 21 31 45 65 58 53 46 41 18 25 421
% with Pus Cells 0 20.5 31.1 32.6 34.3 48.9 44.6 43.4 44.7 42.3 17.8 13.8

Fig. 3.

COMPLICATIONS

Conjunctivitis.—Considering the impossibility of preventing the transfer of pus from the irritated vulva by way of the contaminated fingers to the eyes, especially among the many young children and the mentally deficient girls, it is surprising that not one instance of secondary infection of the conjunctiva occurred among the 381 children studied. There were some patients who were admitted with a diagnosis of gonococcal conjunctivitis who were later shown to have vaginitis also. However, since it appears beyond coincidence that patients with vaginitis did not develop secondary conjunctivitis, it is suspected that infection of the

eye occurs as a primary infection. Therefore, there would be only slight danger of infection of the conjunctiva occurring as a complication of gonococcal vaginitis.

Rectal Infection.—There has been considerable controversy[9, 11] concerning the role of rectal infection in gonococcal vaginitis. Clinical observation and proctoscopic examination of the children studied in this series showed no evidence of a characteristic proctitis although 45 per cent of untreated and estrogen treated patients had positive rectal cultures at some time in the course of their gonococcal infection. Often in these children with positive rectal cultures the rectal mucosa appeared perfectly normal, although sometimes a mucopurulent exudate was present. It is possible that in some of the untreated patients the recurrence of positive vaginal cultures indicated reinfection from the rectum.

The course of the rectal infection when untreated is similar to the course in the vagina. However, no correlation could be determined between the time of spontaneous cure of the rectal and the vaginal infection. Estrogenic treatment for the vaginitis had no effect on the course of the rectal infection when present. In every instance, when a sulfonamide was effective for the vaginal infection, the rectal infection responded also.

Abdominal Complications.—Episodes of acute lower abdominal pain occurred in about 5 per cent of the girls during the acute stage of vaginitis. Although diagnosis of the underlying pathology was difficult, it was evident that extension of the inflammatory process was the cause of these symptoms.

Arthritis.—Gonococcal arthritis occurs rarely in children. It was a complication in only three patients, occurring in an elbow in one and in the knee joint in the other, and in an ankle in the third. Gonococci were identified on culture of the knee joint fluid.

TREATMENT

The results of treatment of vaginitis with various agents were evaluated by comparison with the course of the untreated disease (Fig. 4). Estrogenic substance[12, 13, 14, 15] in the form of vaginal suppositories and stilbestrol given orally, produced clinical improvement but did not shorten the course of the infection as shown by the persistence of positive cultures.

Sulfanilamide[16, 17] was effective in 43 per cent of fifty-three cases, producing a prompt cure clinically and bacteriologically. Sulfapyridine[9] and sulfathiazole[18] proved to be superior to sulfanilamide, curing within one week 87 per cent of the seventy-seven patients treated. The response to chemotherapy is dramatic; all clinical symptoms of discharge, external irritation, and inflammation subside rapidly, and smears and cultures become negative after twenty-four hours of treatment.

Few toxic reactions (gastrointestinal symptoms, skin eruptions, fever, and anemia) occurred with sulfanilamide and sulfapyridine, but none were encountered in any case treated with sulfathiazole. For this reason and because of its high degree of effectiveness, sulfathiazole may be considered the treatment of choice for gonococcal vaginitis. The dosage found to be most satisfactory is ½ gr. per pound of body weight with a maximum of 30 gr. divided into three to six doses, given daily for seven days. Some children who had recurrences of the infection responded to a second course of treatment.

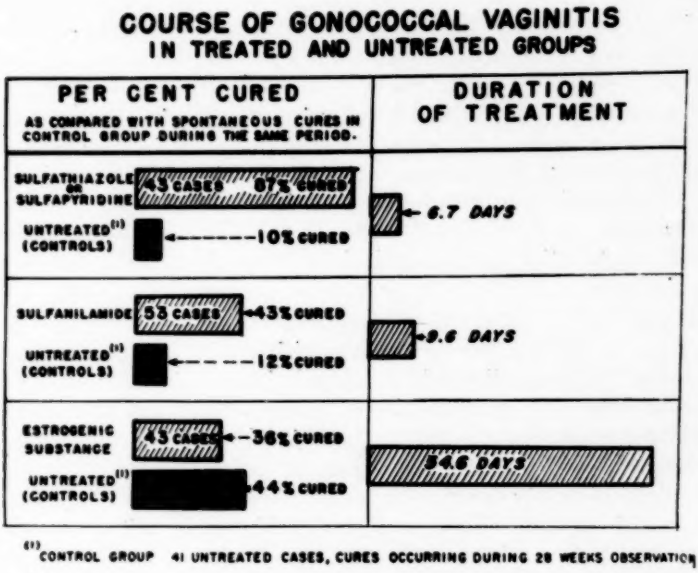

Fig. 4.

CRITERIA OF CURE

Determination of cure of gonococcal vaginitis depends upon repeatedly negative vaginal cultures. Clinical signs and smears cannot differentiate infected from noninfected cases as was demonstrated in the observations reported above. Positive cultures may persist or recur without any clinical signs of vaginitis and with negative smears. In the ten patients considered as failures to sulfathiazole or sulfapyridine therapy, the first positive culture was found in an average of eight weeks after treatment. This indicates that prolonged observation is necessary before statement of cure can be made. It should be noted that every child in the treated groups who became positive at any time after having been negative was classed as a relapse, regardless of the possibility of reinfection.

Various methods have been tried as provocative tests of cure[6] in children who had apparently responded successfully to treatment. Nothing has proved uniformly satisfactory in producing positive findings, even in patients who were subsequently found to be positive. It is only by repeated cultures over a period of months that a cure can be confirmed.

It is therefore suggested that a follow-up period of at least six months with vaginal smears and cultures at monthly intervals should be used for the criteria of cure. Cultures also should be taken whenever suggested by suspicious clinical findings.

EPIDEMIOLOGY

The generally accepted impression that gonococcal vaginitis is an extremely contagious disease among young girls has especially concerned hospitals and child-caring institutions. For this reason routine admission examination of female children by the smear method has been required, and rejection of those with "suspicious" findings has been the rule. However, as will be shown, the epidemiologic study of this series has indicated that gonorrhea is no more contagious in children than in adults. There is no reason to believe that a child can develop a vaginal infection unless pus containing gonococci reaches the region of the vulva.

Many children attended school for some time before they came under observation and were excluded. It is known that many children attend school during the entire course of a gonococcal infection. Yet during the three years of this study there was no evidence of a school epidemic. There was no distribution of these cases that could be related to any particular school.

In a hospital ward where this study was conducted there were patients with acute gonococcal vaginitis, children who were cured of this infection, and others who had been admitted for diagnosis and were found free from infection. Except for good nursing technique in the care of these children, no isolation precautions were instituted. The children mingled freely on the ward, in the schoolroom and on the playground. During the past five years there has been no instance of infection of a cured child or a child admitted for observation. At some times all the children used the same toilet without the occurrence of a new infection. Many attempts to recover gonococci on culture from toilet seats immediately after use by infected children were unsuccessful except in one instance.[6]

Further observations were made in an overcrowded institution for the feebleminded[19] where isolation technique was impossible and semitrained attendants rather than nurses cared for the children. Only 2 of 115 girls in one cottage were found to have a gonococcal infection. In another cottage, 25 of 146 children were positive on culture examination.

In this institution gonococcal vaginitis showed no epidemic characteristics. The findings point instead to transfer of the infection from patient to patient as a result of breaks in nursing technique.

There was no epidemic of gonococcal vaginitis in any institution in New York City during the three years of this study. Infections which did occur in the institutions studied suggested that these were the result of direct transmission of pus from an infected child to a healthy one through some break in care. Two children who had positive cultures but no clinical signs of infection were allowed to return to an institution. A close check revealed no secondary cases.

Examination of the adult contacts of gonococcal vaginitis cases revealed that over 50 per cent had the infection without being aware of it. Adding to this number the contacts who were under treatment gave a high per cent of cases where the possible source of infection could be traced to a parent or sibling. Further evidence of the mode of infection was obtained by the history of sex play or actual intercourse shortly preceding the onset of vaginal discharge in 35 per cent of the children over 6 years of age who were questioned.[9]

From these observations it is apparent that vaginitis will not spread from one girl to another when ordinary precautions are taken to prevent the vaginal discharge of an infected child from reaching the vulva of the noninfected. Attention should be directed toward contaminated linen, diapers, rectal thermometers, enema tips, etc. The contaminated fingers of the parent or attendant are probably the most frequent fomites in the transmission of the disease. Toilet seats are not an important factor.

CONCLUSIONS

The findings reported by this study seem to justify the conclusion that:

Culture is the best method for diagnosis and statement of cure in gonococcal vaginitis.

Sulfathiazole is the treatment of choice.

Patients with vaginitis who require hospitalization may be cared for on general wards with the usual isolation technique which is applied in other slightly communicable diseases.

Treated patients may return to schools and institutions as soon as clinical signs have cleared and cultures are negative.

Negative findings on monthly examinations over a period of six months following treatment are a satisfactory standard of cure.

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TUBERCULIN PATCH TEST

Study of Effect of Variations of the Normal Procedures

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WITH the growing popularity and increased use of the tuberculin (Vollmer) patch test and with its acceptance by the Council on Pharmacy and Chemistry of the American Medical Association, the question of its flexibility under varying circumstances naturally is important and should be definitely determined.

Notwithstanding a few[1-3] unfavorable reports, its advantages[4-10] and its accuracy[4, 6, 7, 9-19] when performed as directed have been very well covered in the literature and need no further repetition.

The purpose of this paper is to determine whether certain variations of the method prescribed would affect the result and to what degree.

Those variations were determined by trying to simulate conditions that might arise in a clinic, hospital, physician's office, or at the home of a patient.

With this in mind, the various changes made were as follows:

1. The patch was directly applied to the skin without any preparation of the area at all.
2. Alcohol was used to cleanse the skin area before applying the test.

In the remainder, the patch was altered as noted in each instance but otherwise was applied in accordance with normal procedures.

3. The patch was kept in the incubator for forty-eight hours.
4. The patch was autoclaved for one-half an hour.
5. Autoclaved for one hour.
6. Autoclaved for two hours.
7. Autoclaved for four hours.
8. Autoclaved for six hours.
9. Exposed to ultraviolet rays for fifteen minutes.
10. The patch was removed from its cellophane wrapper and exposed to the air of the room for one month.
11. Alcohol was dropped, to cover fully the tuberculin squares of the patch, and allowed to dry and then repeated; i.e.; alcohol was applied twice.
12. Treated with alcohol as in No. 11 but for four times.
13. The patch was dipped into alcohol, immediately removed and dried.

From the Pediatric Service of Metropolitan Hospital, New York City; Dr. Reuel A. Benson, Director.

14. Placed into alcohol for one hour, removed and dried.
15. Dipped into water, immediately removed and dried.
16. Placed under water for one hour, removed and dried.
17. Dipped into acetone, immediately removed and dried.
18. Left in acetone for one hour, removed and dried.

The standards established for reading all reactions were as follows:

One Plus (+).—An erythematous area, sharply defined and corresponding in size to the tuberculin treated square.

Two Plus (++).—An erythematous area with slight elevation above the surrounding surface but limited to the tuberculin treated square and occasionally associated with very fine pinpoint vesicles.

Three Plus (+++).—A markedly erythematous area definitely elevated and the erythema extending slightly beyond the square and some small vesicles in the area.

Four Plus (++++).—Marked erythema and elevation both extending beyond the treated square with numerous vesicles noted.

Whenever the reactions of the two sides of the patch varied, the strongest reading was the one accepted.

In comparing the sensitivity of each variation as compared to the original tuberculin patch, a standard called the patch sensitivity quotient (PSQ) was formulated by one of us (J. S.) in order to simplify the procedure. This was arrived at by reading each test as varying from one to four plus, depending on its severity as previously mentioned. Then the sum of the regular Vollmer patch readings was used as the denominator and that of each variation as the numerator. A result of one or greater than one would indicate that the change attempted had had no deterrent effect, while any figure less than one would indicate the degree of inferiority in doing the test under the given condition.

The explanation for some of the results that were greater than one might be on the basis that the regular test had been done prior to the variation test in some cases, that the sensitivity of the patient may have increased, or that the value of direct comparison was lost in not having done them simultaneously.

With the above factors in mind, the results obtained are listed in Table I, each number listed corresponding to the variation as numbered above.

In addition, six of the children who had regular patch tests on their backs were placed in bathtubs and water was thrown over them so as to soak the region of the test. On removal from the tub it was necessary to be sure that the patch was in apposition to the skin or else another piece of adhesive had to be used to re-enforce it. In all of these cases, the sensitivity of the patch test was unaffected.

TABLE I

EFFECT OF VARIATIONS ON PATCH SENSITIVITY

TYPE OF VARIATION	NUMBER OF TESTS	PATCH SENSITIVITY QUOTIENT
1	21	0.94
2	14	1.05
3	10	0.89
4	10	0.89
5	12	0.92
6	13	0.81
7	7	0.73
8	5	0.50
9	11	1.13
10	13	1.02
11	22	1.06
12	8	1.00
13	14	1.03
14	7	0.95
15	9	0.96
16	7	0.95
17	9	0.92
18	7	1.00

At this point it should be added that whenever the adhesive lost its stickiness, especially when autoclaving four and six hours and following lengthy immersion in fluids, it was re-enforced by new adhesive. It should also be noted that some of those soaked in alcohol, acetone, and water gave a wider area of reaction and sometimes, but not always, extended over into the control.

Three control tests for each of the patch modifications[3-18] were done on normal nontuberculin reacting children and not one reaction was obtained.

Another point worth mentioning and which was noted during this study was that positive reactions were often still evident from two to twenty weeks after removal of the patch.

Despite the contention[4, 7, 9, 11, 19] that no constitutional reactions occur, in this group of fifty-one tuberculin-positive children that were studied, four (7.84 per cent) had some systemic reaction; namely, temperature. It should be observed of course that in most of the cases, and including the four mentioned, four patch tests were done simultaneously.

In the four patients that reacted, the temperature rose from within several hours to two days after the tests were applied, varied from 100.6° to 102°, and lasted from twelve to forty-eight hours.

X-rays and blood sedimentations were done, but they failed to show any definite activation or progression of the process.

SUMMARY AND CONCLUSION

1. Eighteen variations of the Vollmer patch test technique were tried on fifty-one tuberculin-positive children.

2. The efficiency of the test decreased in direct proportion to the amount of autoclaving or incubation.

3. All other variations attempted had from very slight to practically no deleterious effect on the result.

4. Skin reactions did not fade until two weeks had passed and some were still visible after twenty weeks.

5. Thermal constitutional reactions occurred in four (7.84 per cent) cases, but no objective evidence of activation could be obtained.

6. Therefore, it was concluded that the Vollmer patch test was very stable under the given circumstances except for heat, and that its application was attended with no objective detriment to the patients.

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BENZEDRINE SULFATE (AMPHETAMINE) IN THE TREATMENT OF OBESE CHILDREN AND ADOLESCENTS

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OBESITY results from excessive intake of food, from decreased muscular activity, or from a combination of the two. In our observation both factors play a role in most cases.[1] For effective weight reduction, both dietary restriction and increased physical exercise are necessary. From a mechanical point of view, the problem appears to be a simple one. Yet obese patients, even if anxious to lose weight, show a singular disinclination to follow advice and to change their eating and living habits. Help is expected from some drug which will melt away the burdensome fat, without effort on the part of the patient. This problem seems to be as old as recorded history itself. The ancient Greeks credited the Cretans with knowledge of the ideal drug which would cure obesity without disturbing gluttony.[2] The secret of this drug has been lost and modern medicine is still searching for a safe way of easy weight reduction. As long as it was assumed that a "lowering" of the basal metabolism was the cause of obesity, calorigenic drugs were widely recommended. The administration of thyroid has been extremely popular, and it is abandoned only with great reluctance in spite of its ineffectiveness.

More recently the search has been directed toward a drug which would depress the inordinate appetite of the obese and would thus insure a lowering of the caloric intake. Many pharmacologic effects are accompanied by loss of appetite, and all kinds of drugs are occasionally recommended for this action.[3] Yet the margin of safety is so narrow that these attempts are generally short-lived. During the past few years a number of authors[4] have reported on the favorable effect of benzedrine sulfate, which is supposed to act by decreasing appetite and increasing physical activity.

The published results appear to be uniformly favorable, so that one is encouraged to consider benzedrine sulfate as a drug of specific value in the treatment of obesity. However, the reports are not entirely conclusive because the possible influence of other factors has been more or less neglected. The statement that a renewed increase in weight followed interruption of treatment is not in itself proof of a specific effect of the drug if the other conditions of the whole treatment have not

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been kept equal. Low caloric diets are simultaneously prescribed by most authors, and the patients are checked at weekly or fortnightly intervals. In evaluating the effect of dietary restriction in obese children,[1a] it was found that the result stood in a direct relationship to the regularity of attendance. In evaluating the specificity of any drug therapy in obesity, the effect of the greater regularity and of the closer personal contact with the patient (or therapist) has to be evaluated. The suggestive value of receiving some "pills" must also be considered. It is not unusual that an obese patient asks for the renewal of some prescription which had been given for some incidental reason, because he feels that it has helped him to follow his diet more closely.

The present report will be restricted to recording our experience in the course of one year of the effect of benzedrine sulfate on the weight of obese children and adolescents without going into any discussion of its possible mechanism of action. Particular consideration will be given to the possible suggestive effect of the drug administration and to other factors determining regularity of attendance and cooperation with a low caloric diet.

PLAN OF OBSERVATION

In order to differentiate between true drug action and its suggestive effect, the patients received, alternating with the tablets which contained benzedrine, placebos which in outer appearance and taste so closely resembled the true tablets that no child discovered that different tablets were being issued.* The amount during the experimental period was uniformly one tablet per day (10 mg. benzedrine sulfate), three-quarters (7.5 mg.) of which was to be taken at breakfast time, and one quarter (2.5 mg.) at lunch time. In two patients (Cases 12 and 17) 1½ tablets (15 mg.) were given during the later periods. At each visit seven tablets were handed out by the dietitian; at the same time the weight was checked and dietary adjustment was discussed. The patients were instructed to return every week for check-up and more tablets. Medical examination was given at the beginning of the course and every three or four weeks. Since the visits to the dietitian's office were free of charge, failure to return for financial reasons was reduced. If a patient broke an appointment, he had no tablets for the following weeks. In the subsequent computation only the weeks are counted for which the patient had received tablets. In exceptional circumstances (holidays, school examinations, etc.) tablets for two weeks were handed out. In one instance (Case 7), when the traveling distance was unusually long and the mother pleaded for help in reducing the child's weight, a four-week supply was given for the last two periods.

After a patient had received tablets of one kind four times he was automatically shifted to the other variety. Since any new treatment is

*The benzedrine sulfate and placebo were supplied by the Smith, Kline and French Laboratories, Philadelphia, through the courtesy of Robert E. Turner.

apt to produce an impressive loss of weight during the first few weeks, some patients received benzedrine tablets as first medication; another group was begun on placebos and later changed to drug-containing tablets. The four-week periods were alternated as long as the patients returned to the clinic. The experiment was started in the fall of 1939, and new patients were added throughout the winter until the spring of 1940. The two months of summer vacation, during which the obesity clinic is closed, were planned as a control period, to learn how far the patients had benefited from the previous treatment and were able to hold their weight without treatment.

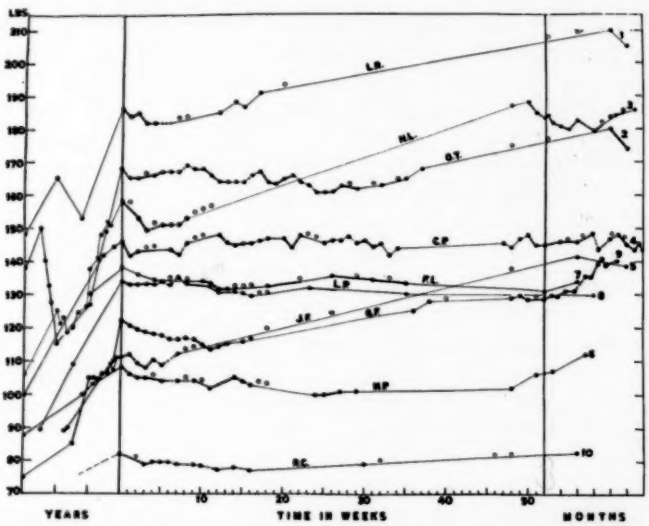

Chart 1.—Changes in weight of patients beginning treatment with benzedrine (Groups 1 and 2 of Table I, omitting Case 11).

The passage of time is represented in weeks for the one-year period of this study, in years for the past history, and in months for the subsequent observation. The graph for each patient is designated by his initials and the number in the table. Periods of benzedrine administration are indicated by heavy lines, periods of placebo by interrupted heavy lines. Each visit to the clinic is indicated by a dot; a broken appointment, by an open circle above the line.

Each of the two groups contained new patients who attempted weight reduction for the first time, as well as old patients who had been under observation for some time. Most of the old patients had been active in previous years and had come for a follow-up examination. Renewed treatment was suggested to those who had gained excessively during the preceding year. A few old patients had been under treatment during the preceding year but had failed to lose weight, or had even continued to gain. In Table I, Group 1 designates old patients in whom treatment was begun with benzedrine, Group 3 the old patients in whom the placeboes were given during the first four weeks. Group 2 refers to new patients who received benzedrine during the first period, and Group 4

to those new patients who received placeboes at the onset of treatment. Group 5 represents a control group of children who appeared to be sufficiently interested in weight reduction that one could expect that they would come regularly to the clinic and adhere to the prescribed diet without the incentive of receiving special free medicine.

Selection of patients was determined by their willingness to return regularly. Since young children have to be accompanied to the clinic, and since only a few mothers were willing to come every week, the majority of observations have been made on patients of puberal age who could be trusted to come alone and who also showed an interest in losing weight. It was planned to have six patients in each group. Four patients discontinued treatment during the first four weeks and are not included in the computation.

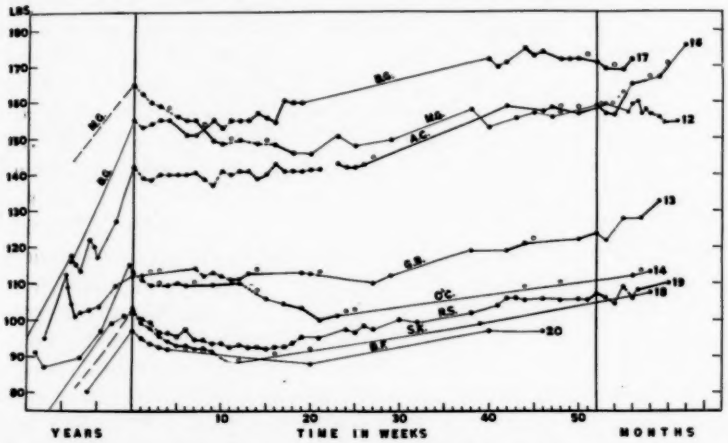

Chart 2.—Changes in weight of patients beginning treatment with tablets containing no benzedrine (Groups 3 and 4 of Table I, omitting Case 15).

The passage of time is represented in weeks for the one-year period of this study, in years for the past history, and in months for the subsequent observation. The graph for each patient is designated by his initials and the number in the table. Periods of benzedrine administration are indicated by heavy lines, periods of placebo by interrupted heavy lines. Each visit to the clinic is indicated by a dot; a broken appointment, by an open circle above the line.

In explanation of the new therapy all patients and their parents received the same information, that we intended to test the effectiveness of a new drug which had helped other obese children in following the diet more closely, and thus had helped them to lose weight; that the drug was without harmful by-effect, but that we wished to check the patient every week. At subsequent visits the patients were questioned about their observations and reactions to the medication. Most patients eagerly confirmed the fact that the pills had helped to curtail their craving for food, yet no child discovered the difference between the drug-containing and inert tablets. In one instance the mother had tried the effect on herself. She enthusiastically described how the pills had

checked her desire to nibble candy. She immediately complained that these new tablets were ineffective when the child received the placebos. The patients in this study were accustomed to discuss freely different aspects of their behavior and daily routine. Information about possible other effects thus could be obtained without suggesting such effects to the patients. Stimulating or undesirable by-effects are conspicuous by their rarity. Some patients said that they were more active, others felt that the tablets made them "kind of weak." Most children, or their parents, failed to register any influence on mood or activity.

RESULTS OF TREATMENT

The results of the experiment are recorded in Table I and are graphically demonstrated in Charts 1, 2, and 3. The table gives information on the age at the time when the treatment was started. Height and weight and percentage of weight excess, calculated from the Baldwin-Wood tables,[5] are recorded in columns 5, 6, and 7. Below the figures indicating the beginning of the observation period are figures recording height, weight, and percentage of weight excess after about one year. The rate of gain during the preceding year (column 8) was calculated from the clinical record or school observations. In a few instances no figures could be obtained. According to the available information, these children had been gaining rapidly. In order to evaluate whether the medication and close supervision had a lasting effect upon the patients' ability to maintain their weight unaided, the increase in weight during the control period was included in the evaluation. The follow-up period varied from twelve to sixty-two weeks and the change in weight is expressed as rate of gain per year. It may be surmised that a patient who gained one pound per week for sixteen weeks (Case 12) would probably not have continued at the same rate for a whole year, or that another patient (Case 22) who lost 1.5 pounds per week during the twelve-week control period would have slowed down or stopped losing weight after reaching his normal weight. By expressing the gain in weight during the follow-up period as rate per year, any change in the rate of gain can be recognized by comparing column 14 with column 8.

The periods during which medication was received are recorded in columns 9 and 10. The number of broken appointments is not included in the table; they are registered on the charts in relation to clinic visits. Only two patients (Case 2 and Case 12) made use of the opportunity to come regularly until summer vacation. All other patients discontinued treatment or broke appointments frequently. Greater regularity was observed in those patients who did not receive medicine but were anxious to reduce. The good cooperation in this group may be explained by the circumstance that those who were not truly interested in treatment did not return at all if no medicine was offered, and are therefore

eliminated from the computation, and that through the bait of some new treatment a number of otherwise uncooperative patients could be induced to accord partial cooperation.

The change in weight during the periods of drug administration is recorded in columns 11 and 12. With one exception (Case 17), all patients lost weight or gained at a much slower rate than during the previous year. In the first two groups, which began treatment on benzedrine sulfate, the loss during the benzedrine period was conspicuously better than during the administration of the placeboes. In Groups 3 and 4, however, when the placebo was given during the first four weeks, the greater loss in weight was registered during the placebo periods. This behavior demonstrates how greatly suggestion and the enthusiasm over a new treatment influences change in weight in obese patients. On the other hand, these two groups showed some loss during the benzedrine periods, indicating that apart from its suggestive value the drug may have some specific effect.

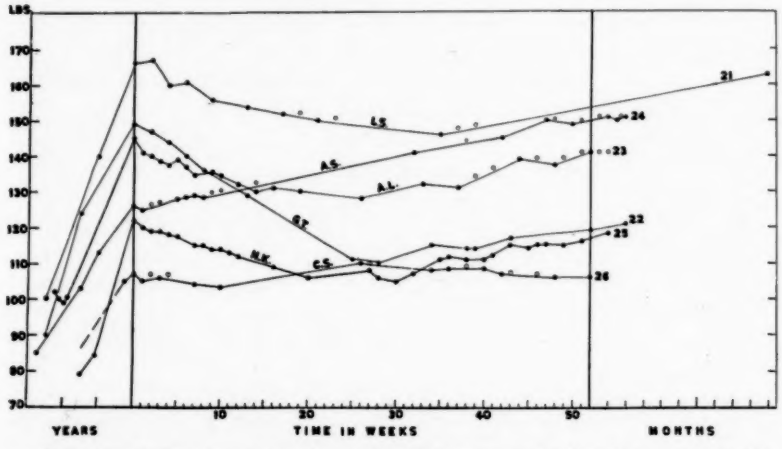

Chart 3.—Changes in weight of patients receiving no medication (Group 5 of Table I).

The passage of time is represented in weeks for the one-year period of this study, in years for the past history, and in months for the subsequent observation. The graph for each patient is designated by his initials and the number in the table. Each visit to the clinic is indicated by a dot; a broken appointment, by an open circle above the line.

If the sum of all treatment periods is considered, disregarding the influence of regularity and first enthusiasm, the figures appear to be in favor of benzedrine. Twenty patients received drug-containing tablets for 142 weeks and showed a combined loss of weight of 60 pounds. These same patients showed a combined loss of 34 pounds during 124 weeks on placeboes. This difference suggests some specific value of benzedrine. However, the weekly losses in weight of all the patients, even when the old and new patients are considered separately, are not significantly higher during the benzedrine administration than during

TABLE I

NO.	INITIALS	SEX	AGE (YR. AND MO.)	HEIGHT (INCHES)	WEIGHT (POUNDS)	OVER-WEIGHT (PER-CENTAGE)	APPROX. GAIN IN PRECED-ING YEAR (POUNDS)	DURATION OF TREATMENT IN WEEKS		CHANGE IN WEIGHT		FOLLOW-UP	
								BENZ.	PLACEBO	BENZ.	PLACEBO	AFTER WEEKS	RATE OF GAIN PER YR.
Group 1													
1	L. R.	M	14;6 15;10	65¾ 68	186 210	55 (50)	26	4	2	-4	0	62	24
2	G. T.	M	14;3 15;9	64 65¼	168 180	46 (45)	41	13	12	-5	-3	38	25
3	H. L.	M	12;9 13;9	60¼ 64¼	158 184	70 66	31	4	2	-7	+2	40	47
4	C. P.	F	12;11 14	62¼ 64	146 147	35 29	11	14	5	-6	+5	13	8
5	J. F.	F	10;6 11;8	54½ 56	112 141	56 81	6*	4	3	-2	+3	53	27
6	H. P.	M	13;9 14;10	57 59¼	108 107	33 19	4*	10	5	-3	-3	21	3
Average						49 49	+20	8.2	4.8	-0.55 per week	+0.01 per week		+22
Group 2													
7	F. L.	F	10;9 11;10	57¼ 60½	138 133	66 37	7	13	0	-3	0	17	-6
8	L. P.	F	11;9 13	58½ 60¼	134 130	52 34	18	8	6	-5	0	48	0
9	G. F.	F	10;3 11;3	55¾ 58¾	122 136	58 53	23	8	5	-6	-1	25	21

10	R. C.	F	6;11 8;3	51¾ 54	82 83	30 18	++†	8	8	-3	-2	44	7
11	R. L.	M	6;6 7;3	48½ 50¼	74 74	40 25	++†	4	4	-3	-1	25	12
Average						49 33	>12	8.2	4.6	-0.49 per week	-0.02 per week		+5.7
Group 3													
12	A. C.	F	11;5 12;5	58 60	142 158	65 66	25	12	12	0	0	16	52
13	G. B.	F	8;7 9;9	53½ 55½	112 122	65 62	8*	2	7	+2	-2	22	38
14	O'C.	M	9;2 10;5	55½ 58	112 112	51 33	18	6	6	-3	-3	36	15
15	A. T.	F	9;6 ----	52½ ----	110 ---	72 --	17*	4	8	-1	+1	--	--
Average						63 54	+14.5	6	8.2	-0.08 per week	-0.12 per week		+35
Group 4													
16	M. G.	F	11;6 12;6	59½ 63¼	165 157	81 40	+++†	8	8	-10	-9	34	17
17	B. G.	M	11;10 12;10	57½ 60¼	155 172	89 87	25	8	7	+5	0	21	30
18	S. K.	F	8 9;4	55¼ 58¼	103 105	41 23	++†	4	8	-4	-12	38	15
19	R. S.	M	12;6 13;6	57½ 59½	102 105	24 18	7	8	12	-2	-4	22	19
20	B. F.	F	10;5 11;3	52 53	97 97	52 43	12	0	4	0	-5	36	7
Average						57 42	>14	5.6	7.8	-0.4	-0.75		+17.5

Table I—Cont'd

NO.	INITIALS	SEX	AGE (YR. AND MO.)	HEIGHT (INCHES)	WEIGHT (POUNDS)	OVER-WEIGHT (PER-CENTAGE)	APPROX. GAIN IN PRECED-ING YEAR	DURATION OF TREATMENT IN WEEKS		CHANGE IN WEIGHT		FOLLOW-UP	
								BENZ.	PLACEBO	BENZ.	PLACEBO	AFTER WEEKS	RATE OF GAIN PER YR.
Group 5								NO MEDICATION					
21	H. S.	F	10;10 12;7	62½ 63½	166 163	62 46	26	21		-16		14	-11
22	G. T.	M	11;9 12;9	57 60	149 119	88 31	25	13		-20		12	-77
23	A. L.	M	11;3 12;3	60 61½	145 141	59 45	30	16		-14		17	+ 3
24	A. S.	F	10;6 11;7	56¼ 59¾	126 151	60 61	13*	8		+ 2		24	+28
25	H. K.	F	11 12	56¾ 59¼	122 116	49 27	33	16		-14		19	+11
26	C. S.	F	9;6 10;6	55 57	107 106	45 29	+++†	10		- 4		16	+30
Average						60 40	>25	14		- 0.79 per week			- 2.7

*Dietary restriction during the preceeding year.
†Marked gain; exact amount not recorded.

the periods on placebo if the figures are dealt with statistically.* It is possible that the absence of a significant influence of benzedrine in this group of obese patients is due to the fact that the dosage of 10 mg. was insufficient for many patients. We felt that the result warranted further observations with higher dosage. These observations have not yet been completed. As far as they were made on the same patients these later periods of treatment are represented on the charts. They are not included in the table. The results thus far indicate that patients who had shown by their rapid increase in weight during the follow-up period that they had achieved little active control over their food intake were not markedly affected by higher doses of benzedrine sulfate. Cases 9, 13, and 16 continued to gain rapidly during the last few months of observation, in spite of treatment periods with 20 to 30 mg. of benzedrine daily.

In evaluating the efficacy of any therapy in obesity the persistence of the result is of real importance. A patient benefits little from a drastic reduction of weight over a short period if he is unable to maintain his weight later on. The figures for height and weight about a year after the onset of treatment are included to illustrate the real progress of the patient. If one considers a decrease of less than 10 per cent in the weight excess (column 7) or even an increase as no improvement, a decrease of 10 to 20 per cent as moderate improvement, and of more than 20 per cent as marked improvement, one finds that eleven patients were unimproved at the end of one year, nine moderately improved, and five markedly improved. All of these markedly improved children were new patients, two of whom received no medication at all.

If the degree of improvement is compared with the rate of weight loss during the drug administration (loss per week), no correlation can be detected between the subsequent course and the rate of loss during a short treatment period. It was found that the improvement in the condition stands in excellent agreement with the rate of gain during the follow-up period. Thirteen children gained at the same rate or more than before treatment (compare column 14 with column 8); in twelve patients the rate of gain was markedly slower during the follow-up periods than during the preceding year. Only one patient in this latter group failed to show an improvement in the degree of his obesity (Case 2). He had gained forty-one pounds during the previous year. The slower rate of twenty-five pounds during the follow-up period was still too high to result in a change of his condition, particularly since he grew only a little during that period. The evaluation of the factors which interfered with successful treatment in individual patients leads to findings very similar to those which were discussed in detail in a previous publication.[1a] The influence of the factors which cause overeating and interfere with the normal social and emotional development of these children seems to outweigh the possible pharmacologic action of the drug.

*The chi-square method was used in comparing the different groups.

From the psychologic viewpoint there exists the danger that the patient may become passively dependent upon receiving pills and attention without developing any active self-control (Case 12).

Though the findings in this study encourage further observation on the effect of larger dosage under comparable experimental conditions, our experience thus far does not warrant the general usage of the drug in unselected obese patients. As the experience with the drug increases, it will be possible to set up better criteria for the selection of suitable cases. This understanding of the effect of the drug can be gained only when the influence of other, sometimes quite obvious, factors is recognized as such and is differentiated from the true pharmacologic effect. Without this precaution a drug of probable value is in danger of having a short period of enthusiastic recommendation only to sink into early oblivion by failing to meet exaggerated and impossible expectations.

SUMMARY

The effect of a uniform daily dosage of 10 mg. of benzedrine sulfate on the weight of twenty obese children and adolescents was studied.

In order to evaluate the influence of suggestion and of regular clinic attendance, tablets resembling benzedrine sulfate but containing no drug were given in alternate periods of four weeks.

The loss of weight during the periods of placebo was slightly lower than during benzedrine administration. The difference was not of statistical significance.

The best loss in weight occurred during the first few weeks of treatment. This cannot be explained as drug action but is an unspecific effect depending on the patient's enthusiasm for a new therapy.

The best loss of weight was observed in a control group of children who showed good cooperation and regular clinic attendance without receiving medication.

In evaluating the effect of any medicine on the appetite and weight of obese patients, the influence of other factors, such as suggestion and better cooperation, has to be differentiated from the true pharmacologic effect.

Although this study did not show a significant influence of 10 mg. benzedrine sulfate upon the weight loss, the findings encourage further observations of the effect of larger dosage.

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THIAMIN CONTENT OF VARIOUS MILKS

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PRIOR to 1938 biologic assay was the only method available for the determination of thiamin in milk. Since that time there have been several reports of determinations by chemical methods; most of these are modifications of Jansen's method.[1] By Jansen's method thiamin is oxidized to thiochrome by alkaline potassium ferricyanide; the thiochrome is then extracted with isobutyl alcohol. The alcoholic solution of thiochrome fluoresces in the presence of ultraviolet light, the amount of fluorescence being measured quantitatively in a fluorimeter.

In Neuweiler's method[2] the fat of the milk is removed by centrifugation. The milk is then brought to a pH of 3.5 and heated in a water bath for eight minutes; pepsin is added and the milk incubated for twelve to sixteen hours at 37° C. The thiamin is then adsorbed on franconite. After an hour it is removed and treated with alkaline potassium ferricyanide and isobutanol. Widenbauer and Heckler[3] omit the pepsin digestion and the adsorption of thiamin on franconite; the oxidizing agent and isobutanol are added directly to the milk. The isobutanol layer containing the thiochrome is separated and filtered. Hennessy and Cerecedo[4] precipitate the proteins of milk with trichloracetic acid. The thiamin contained in the filtrate is adsorbed on permutit and removed by 25 per cent solution of potassium chloride. The potassium chloride eluate is treated in the usual manner by oxidation and extraction. In a subsequent publication, Hennessy[5] advises that the milk be hydrolyzed with 0.5 per cent taka diastase at a pH of 4 to 4.5 and at a temperature of 50° C. for two hours. The material is then adsorbed on permutit and treated as described in the earlier publication.[4] In Pyke's method[6] the milk is digested overnight with pepsin and then with taka diastase for five additional hours. Houston[7] advises treating milk with taka diastase, stating that such digestion almost doubles the fluorimetric assay. Salter[8] incubates milk with taka diastase for three hours at 37° C. Conner and Straub[9] hydrolyze the food product with clarase for two hours at 45° C. The vitamin is then adsorbed on permutit and treated in a manner similar to that described by Hennessy and Cerecedo.[4]

Based on experimental study of these modifications, a method is here presented for the determination of thiamin in milk which is accurate,

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specific, and easy to perform. In addition, data on the thiamin content of cow's milk and of various modifications of it as well as preliminary data on the thiamin content of human milk are presented.

EXPERIMENTAL

Method.—To 5 c.c. of milk which have been brought to room temperature, 25 mg. of taka diastase and 0.2 to 0.3 c.c. of 10 per cent acetic acid are added. The mixture is incubated for one hour at 37 to 38° C.; during this period it is agitated several times. After incubation, 0.1 c.c. of 1 per cent solution of potassium ferricyanide and 3 c.c. of 15 per cent solution of sodium hydroxide are added. The tubes are shaken and allowed to stand for two minutes; 13 c.c. of isobutyl alcohol are then added and the tubes shaken vigorously for one minute. Centrifugation for five to ten minutes separates the isobutanol from the aqueous layer. The isobutanol is placed in the cuvette of the fluorimeter, and the amount of fluorescence is measured. Blanks must be run with each specimen of milk. These are treated exactly as the sample except that the potassium ferricyanide is omitted and the order of addition of sodium hydroxide and isobutyl alcohol is reversed. The reading of the blank is subtracted from that of the sample as it represents the fluorescence due to the reagents and to the nonthiochrome fluorescent substances in the milk.

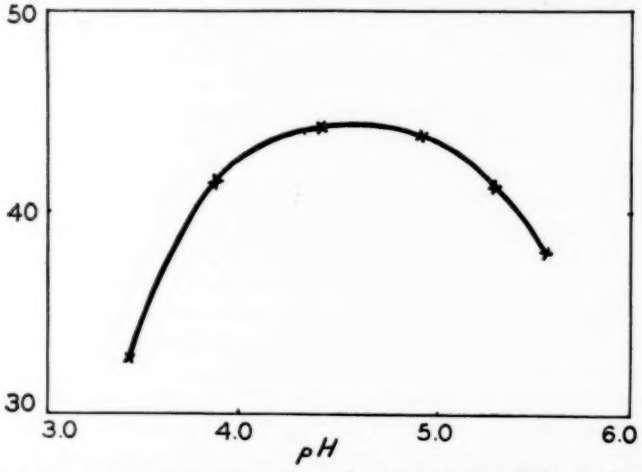

Fig. 1.—Influence of pH on hydrolysis of bound thiamin by taka diastase. Ordinates represent galvanometer deflections. Twenty-two units equal 1 μg of thiamin.

INFLUENCE OF PH

There is lack of agreement concerning the pH at which the activity of taka diastase is greatest. Houston[7] advises a pH of 3.7 to 4; Hennessy,[5] 4 to 4.5. The range of pH for optimum activity, as shown in Fig. 1, is between 4 and 5. It has been found that the addition of 0.2 to 0.3 c.c. of 10 per cent acetic acid will reduce the pH of 5 c.c. of cow's milk to the proper acidity. Because of the lower protein content of human milk, 0.1 to 0.2 c.c. of 10 per cent acetic acid is sufficient for correction of the pH of a 5 c.c. sample.

ACTION OF TAKA DIASTASE AND PEPSIN

In Fig. 2 are shown the comparative values of thiamin per 5 c.c. of cow's milk employing 10 and 25 mg. of taka diastase. Samples of milk containing each of these quantities of taka diastase were kept respectively at 37° to 38° C. and at room temperature (21.5° C.) for the specified periods of time. The amounts of thiamin found in the specimens kept at room temperature were slightly lower for the first thirty and sixty minutes than in the corresponding incubated specimens. After the first hour the differences fell within the range of experimental error.

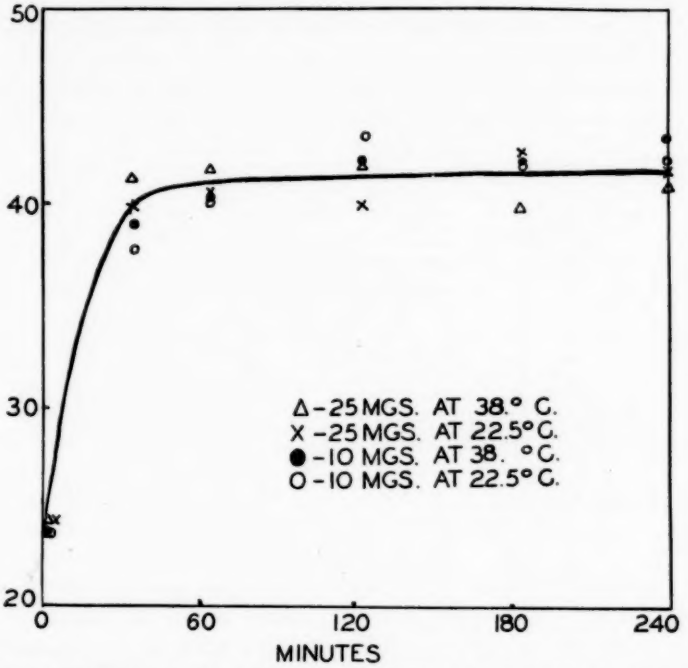

Fig. 2.—Effect of concentration of taka diastase and of length and temperature of incubation upon hydrolysis of bound thiamin. Ordinates represent galvanometer deflections. Twenty-two units equal 1 μg of thiamin.

The specimen incubated with 25 mg. of taka diastase reached the maximum value within a shorter period of time. This observation has been confirmed by repeated determinations. In specimens containing 50 and 100 mg. of taka diastase, values similar to those with 25 mg. were obtained. Incubation of the specimens at 50° C. for two hours also yielded values similar to those specimens incubated at 38° C. for one hour. The taka diastase employed is an aqueous solution, 1 c.c. of which contains 25 mg. This solution will retain its potency for at least one week but may become turbid unless kept at 5° C.

Digestion of milk with pepsin failed to produce any increase in the amount of thiamin recovery. The values obtained when 5 c.c. of cow's milk were incubated at a pH of 1.5 to 2 for as long as twenty-four hours with 150 mg. of pepsin were similar to those obtained when the milk was treated directly with potassium ferricyanide and alkali without any preliminary incubation.

FORM AND STABILITY OF THIAMIN IN MILK

Houston[7] states that the thiamin in milk is present in both free and combined states. He believes, on the basis of ultrafiltration experiments, that the bound thiamin is in combination with protein. He does not believe the thiamin combined with protein to be co-carboxylase. If the bound portion is attached to the protein, the combination must be a loose one, for, as shown in this study, the bound thiamin is found in the filtrates when the proteins are precipitated with either trichloracetic acid or ammonium sulfate.

TABLE I

STABILITY OF THIAMIN IN COW'S MILK KEPT AT 5° C.

DAY	READINGS
0	39.9
1	39.6
2	40.8
3	40.4
4	38.0
5	38.2

Figures represent galvanometer deflections of 5 c.c. specimens.
A deflection of 22 units represents 1 μg of thiamin.

Thiamin in fresh cow's milk is fairly stable. In Table I are shown the values obtained on the same specimen of cow's milk tested daily for five days, during which time it had been refrigerated at 5° C. There is no significant difference in the values obtained, the variations being within the limits of experimental error. Thus, thiamin determination on specimens of milk may be deferred for several days providing the specimen is kept at 5° C.

MATERIALS

The cow's milk, secured from the hospital's supply, is delivered to the institution by the dairy within twenty-four to forty-eight hours after milking. It is pasteurized "B" milk of which 80 to 85 per cent is derived from a Holstein breed of cows; the rest is from various other breeds. The other grades of fresh milk and the milk preparations were secured on the open market. The evaporated milks were diluted with equal quantities of water; the dried cow's milk preparations were reconstructed by the addition of water according to the directions of the manufacturers. To 2 c.c. of the reconstructed preparation, 3 c.c. of

water were added and the sample tested for thiamin. If larger quantities of the reconstructed milk are used, an emulsion is formed upon shaking with isobutyl alcohol, making it difficult to separate the isobutanol from the aqueous layer. Five cubic centimeter specimens of cow's milk and human milk were utilized for analysis. Centrifugation and the removal of fat of human milk are necessary because the milk is often yellow during the first few days of lactation. This yellow pigment is extracted by the isobutanol and interferes with the measurement of fluorescence. The breasts of the lactating women were pumped at the specified time of feeding and an aliquot of the entire amount obtained was taken for analysis. The subjects were ward patients, thus belonging in the low income group. No attempt was made to correlate the nutritional status nor the thiamin intake of these women with the thiamin content of their milk, nor were they given supplements of thiamin chloride.

RESULTS

While there is general agreement between the values obtained by bio-assay and by chemical methods for fresh cow's milk, this is not the case for modified milk preparations. Munsell[10] states that there is little loss of thiamin during evaporation or drying of milk. Houston,[11] employing a chemical method, observed a 10 per cent loss of thiamin during pasteurization of milk, and Daniels[12] states that evaporated milk contains 60 per cent less thiamin than raw milk and, in a more recent publication,[13] reports a loss of 39 to 54 per cent of the thiamin after the milk is evaporated. Schlutz and Knott[14] found 20 to 34 per cent less thiamin in milk after evaporation, and a further reduction to 58 to 62 per cent after the evaporated milk had been stored at room temperature for eight months. The latter two investigators employed biologic assay. Booher and Hartzler,[15] also employing bio-assay, found 51 μg of thiamin per 100 Gm. of evaporated milk, indicating a loss of 45 per cent of thiamin. Dried milks have been assayed biologically and found by Booher and Hartzler[15] to contain 315 μg of thiamin per 100 Gm., and by Munsell[16] to contain 360 μg per 100 Gm. Employing a chemical method, Pyke[6] reports 255 μg. of thiamin per 100 Gm. of dried milk; Salter[8] finds 0.39 μg. of thiamin per cubic centimeter of reconstructed dried milk. The thiamin content of human milk is reported by Neuweiler[2] to be between 10 and 24 μg. per 100 c.c. and by Widenbauer and Heckler[3] to be between 2 and 36 μg. per 100 c.c.

Cow's milk secured from the hospital's supply contains between 35 and 40 μg. or 12 to 13 international units of thiamin per 100 c.c. This value is similar to those quoted by various authors as shown in Table II. Recovery of added thiamin is between 93 and 102 per cent. In Table III are shown the values of several samples of cow's milk and human milk and the percentage recovery of added thiamin. In Table

TABLE II

VALUES OF THIAMIN IN COW'S MILK TAKEN FROM THE LITERATURE

AUTHOR	VALUES (μG. PER 100 C.C.)
1. Neuweiler[2]	24 to 57
2. Widenbauer and Heckler[3]	13 to 57
3. Hennessy and Cerecedo[4]	38 to 51
4. Houston and Kon[17]	36 to 60
5. Pyke[6]	30
6. Morgan and Haynes[18]	27 to 32*
7. Markuze[19]	30*
8. Schlutz and Knott[14]	29 to 37*
9. Baker and Wright[20]	69*
10. Booher and Hartzler[15]	48*
11. Kendall	35 to 40

*Values obtained by biologic assay; others by chemical assay. Where necessary, values have been changed to micrograms per 100 c.c.
It was assumed that one international unit equals 3 μg.

TABLE III

RECOVERY OF THIAMIN ADDED TO MILK

SPECIMEN	μG. PER 5 C.C. INITIAL VALUE	μG. ADDED	μG. FOUND PER 5 C.C.	RECOVERY (%)
Cow's milk No. 1	1.77	1	2.76	99
Cow's milk No. 2	1.76	1	2.69	93
Cow's milk No. 3	1.70	1	2.63	93
Cow's milk No. 4	1.77	1	2.73	96
Human milk No. 1	0.45	1	1.39	94
Human milk No. 2	0.04	1	1.06	102

TABLE IV

THIAMIN CONTENT OF COW'S MILK AND OF EVAPORATED AND DRIED MILK

TYPE OF MILK	μG. OF THIAMIN PER 100 C.C.
I. COW'S MILK	
1. "B" pasteurized	35 to 40
2. "B" raw	41
3. "A"	37
4. Homogenized	43
5. Certified pasteurized	38
6. Certified raw	45 to 48
II. EVAPORATED MILK	
1.	27
2.	25
3.	18
III. DRIED MILK	
1.	16
2.	20
3.	22
4.	24
5.	26
6.	27
7.	28
8.	38
9.	38
10.*	79

*Fortified with thiamin. Values for the evaporated and dried milks are averages of several determinations on two to three specimens of each preparation.

IV are shown the thiamin values of several grades of fresh cow's milk, three brands of evaporated milk, and ten preparations of dried cow's milk. The market milk tested contained between 35 and 40 μg. of thiamin per 100 c.c.; homogenized milk contained 43 μg., and certified raw milk contained between 45 and 48 μg.

Pasteurization destroys between 10 and 20 per cent of the thiamin contained in milk. Samples of market milk tested before and after pasteurization were found to contain 41 and 37 μg. of thiamin per 100 c.c., respectively; samples of certified milk were found to contain 48 and 38 μg. of thiamin per 100 c.c. before and after pasteurization.

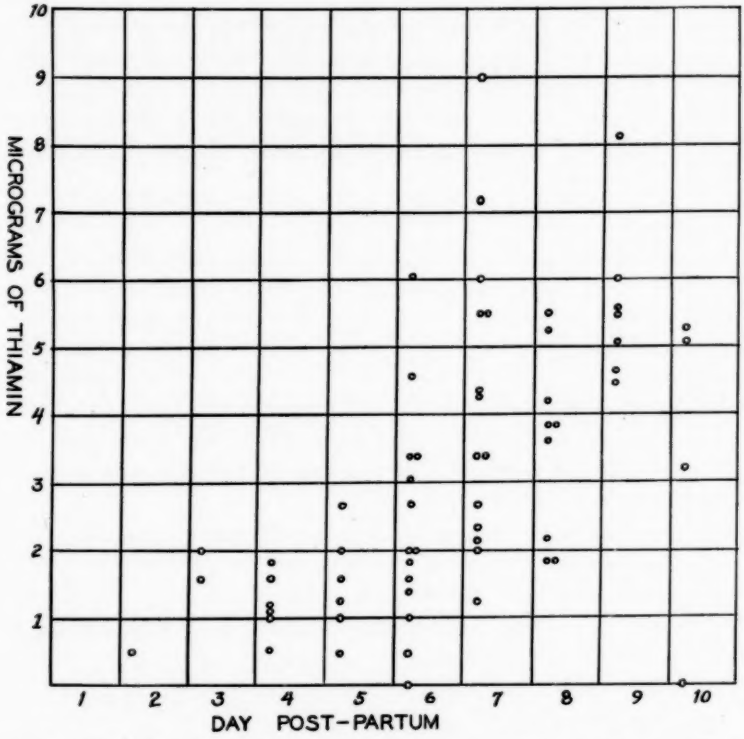

Fig. 3.—Scattergram of thiamin values in micrograms per 100 c.c. of human milk.

The evaporated milks when reconstructed to simulate fresh milk contained 18 to 27 μg. of thiamin per 100 c.c.; this value is 25 to 50 per cent less than that for fresh milk. The different values obtained for the three specimens tested may be explained by the fact that the specimen yielding the least amount of thiamin may have been stored for a longer period of

time. The majority of the reconstructed dried milks contained 40 to 70 per cent of the amount of thiamin found in fresh cow's milk. Product No. 10 contained a large amount of thiamin in comparison with other dried milks; this is explained by the fact that the manufacturer adds crystalline thiamin to the product.

Fig. 3 is a scattergram of thiamin values for 63 specimens of human milk obtained from 32 women, plotted according to the post-partum day on which the milk was obtained. Specimens from several subjects were obtained on successive days. While the quantity of thiamin varies with different specimens, it is consistently lower than that of cow's milk. In two specimens, no thiamin was detected; in four others the readings were so low that the thiamin content was estimated to be less than 1 μg per 100 c.c. The highest value obtained was 9 μg. per 100 c.c. Although the series is small, the scattergram suggests that the thiamin content of human milk tends to increase after the first few days of lactation. The studies on human milk are being continued and will be reported later.

SUMMARY AND CONCLUSIONS

A modification of the thiochrome method has been described for the determination of thiamin in cow's milk and in human milk. The steps in the method consist of incubating the milk with taka diastase, oxidizing the thiamin to thiochrome, and extracting the thiochrome with isobutyl alcohol. This method is simple, accurate, and less time consuming than the methods described by other authors.

Thiamin in milk is present in the free and combined states. Taka diastase liberates the bound portion, enabling it to be oxidized to thiochrome by ferricyanide.

Raw cow's milk contains 41 to 48 μg. of thiamin per 100 c.c. The thiamin content is reduced 10 to 20 per cent by pasteurization. Market milk contains 35 to 40 μg. of thiamin per 100 c.c.

Evaporated milks reconstructed to simulate fresh milk contain 18 to 27 μg. of thiamin per 100 c.c.

Most of the reconstructed dried milks assayed contain 30 to 60 per cent less thiamin than fresh cow's milk.

Human milk early in the lactating period contains much less thiamin than cow's milk. Of sixty-three samples assayed, the thiamin values were found to be between 0 and 9 μg. per 100 c.c. Evidence is presented suggesting that there is a gradual rise in the thiamin content of human milk during the first few days of lactation.

I wish to thank Doctor Robert H. Hamilton of the Department of Biochemistry of Temple University School of Medicine for his advice and counsel in this work.

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TRUNCUS ARTERIOSUS COMMUNIS PERSISTENS

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TRUNCUS arteriosus communis persistens is a relatively rare anomaly. Humphreys in 1932 found fifteen cases in the literature. Since 1932 there have been nineteen instances reported, twelve definite,[2-12, 28] and seven possible instances.[13-18] The details of these cases are presented in Table I.

We recently had an opportunity to study a heart, the seat of transposition with truncus arteriosus communis persistens. This permitted us to re-evaluate our theory of transposition as it applied to the anomaly in question. We therefore present this case with a brief embryologic analysis.

CASE REPORT

Clinical History.—This female infant was born in the thirty-seventh week of pregnancy after a total labor of six hours. At birth she weighed 3,230 Gm. During the first few days of life she had several attacks of cyanosis which subsequently became more frequent and were relieved only by oxygen administration. Physical examination showed an epigastric pulsation; no murmurs were heard. At 18 days of age râles were heard over the lungs, fever developed, and the child died twenty-one days after birth. The clinical diagnosis was congenital heart disease and bronchopneumonia.

Post-Mortem Examination.—In addition to the findings in the heart, the pathologic diagnosis was pulmonary atelectasis and severe passive hyperemia of the lungs, liver, and kidneys.

Description of the Heart.—The heart was globular in shape and distinctly enlarged (Fig. 1). It weighed 20 Gm. The apex was formed by the right and left ventricles. From the base of the heart only one vessel emerged. The mutual relationships of the various heart chambers were normal.

The right auricle was about three times the size of the left and its wall was moderately thicker than that of the opposite chamber. The superior and inferior venae cavae and coronary sinus entered the right auricle normally. The eustachian valve was large and thickened. The Thebesian valve was relatively small. The limbus was well formed, describing a wide arc lined by thickened endocardium, the arc measuring 1.2 cm. in its greatest excursion. The septum primum covered the anterior two-thirds of the ellipse of the septum secundum (limbus), leaving a patency in the foramen ovale measuring 0.5 cm. in greatest diameter. The endocardial lining of the right auricular aspect of the septum primum was greyish white and translucent. The endocardium of the remainder of the right auricle was for the most part thin and transparent, with an irregularly demarcated area of translucency in the region between the auricle and the auricular appendage. The latter was very large, its capacity about equaling that of the auricle itself.

The right auriculoventricular orifice was large and measured 4 cm. in circumference. The valve consisted of only two leaflets, a very large anterolateral leaflet and a smaller medial leaflet. The anterior leaflet was connected laterally to the

From the Department of Pathology of Michael Reese Hospital.
Aided by a grant from the Otto Baer Fund.

normally formed anterolateral papillary muscle, and medially to the normally formed muscle of Lancisi. The medial leaflet, in addition to numerous small chordae connecting it to the septum, was connected to a papillary muscle of moderate size. This papillary muscle originated from the midportion of the inferior (posterior) wall of the right ventricle and obliquely ascended the septum to attach itself to the medial leaflet. No distinct posterior leaflet was noted.

Fig. 1.—View of right ventricle of heart. Note the common truncus emerging from the right ventricle, giving off the coronary arteries, the pulmonary arteries, and the brachiocephalic vessels. The defect of the interventricular septum is present beneath the common truncus.

The right ventricular chamber was about three times the size of the left. Its wall was moderately thickened, measuring 2 mm. in width. The topography of the muscle bundles of the right ventricle was as follows: A septal muscle bundle, which was only slightly thickened, obliquely ascended the upper part of the septum ventriculorum towards the base. Eight-tenths of a centimeter from the origin of the efferent vessel it bifurcated into two limbs of a Y-shaped muscular structure. The small upper limb of the Y fused with the ventricular septum and ascended to the base of the posterior cusp of the efferent vessel. This limb could not be differentiated from the ventricular septum proper. The posterior limb of the Y expanded into a broad structure which formed the base of the commissure between the posterior and right cusps, and of the entire right cusp. Its more posterior (inferior) portion bulged outward in the form of a sharp ridge which pointed towards the commissure between the right and left cusps. Its left margin fused with a small thick triangular muscular structure which lay at the base of the commissure between the right and left anterior cusps of the efferent vessel. This latter muscle bundle was in close relationship to, and also formed the rim of, the anterior two-thirds of the base of the anterolateral leaflet of the right auriculoventricular valve. Between the limbs of the Y-shaped muscle structure there was a quadrangular defect in the interventricular septum measuring 0.6 cm. in diameter. This defect was bounded superiorly (anteriorly) and laterally by the anterior (superior) limb of the Y muscle structure, inferiorly, laterally, and medially by the inferior (posterior) limb of this structure. Superiorly and medially there was a small gap 0.2 cm. in length between the two limbs of the Y. This gap was filled in by a small muscle bundle which originated beneath the medial part of the base of the posterior cusp of the efferent vessel, coursed through the defect of the interventricular septum to terminate on the anterior and basal part of the left ventricular aspect of the septum. In its left ventricular course it formed a rim for the base of the aortic leaflet of the mitral valve. It was thus evident that the defect in the interventricular septum was

TABLE

CASES OF TRUNCUS ARTERIOSUS COMMUNIS

AUTHOR	DATE	AGE OF PATIENT	SEX	ORIGIN OF TRUNCUS	NUMBER OF CUSPS IN TRUNCUS VALVE	EXTENT OF SEPTUM AORTICOPULMONALE
						A. Definite
Beaver[2]	1933	7 days	M	From right ventricle	Four cusps: anterior and right posterior, large; midposterior and left posterior, half-sized and incompletely separated	A beginning of the septum present in view of the single ostium of the pulmonary artery
Carr, Goodale, and Rockwell[3]	1935	36 days	M	From both ventricles, riding over the septum	Two large partially calcified cusps with irregular edges	No septum
Bredt[4]	1935	Not stated	Not stated	From right ventricle	Three cusps: 1 left anterior, 1 left posterior, 1 right anterior; latter small cusp with thickened margins	Small septum
Roos[5]	1935	17 days	F	From both ventricles, riding over septum	4 cusps: 2 anterior and 2 posterior; cusps thickened, translucent, deformed	Semilunar fold divided off pulmonary artery from aorta

*Humphreys summarized the reported cases up to 1932. Not included in her series are two

I

PERSISTENS REPORTED SINCE 1932*

PULMONARY BLOOD SUPPLY	CORONARY BLOOD SUPPLY	CONFIGURATION OF MUSCLE BUNDLES OF RIGHT VENTRICLE	OTHER ANOMALIES	REMARKS
Cases				
Single pulmonary artery which immediately divided into two branches	Coronaries arose from right and left posterior sinuses of Valsalva; no further description given	Photograph shows a large septal muscle bundle and a very small or absent parietal muscle bundle	Cardiac: Defect of the ventricular septum; patent foramen ovale; 4 brachiocephalic vessels; no ductus arteriosus Extracardiac: Aplasia of left kidney and ureter; accessory pancreas in duodenum and ileum; accessory spleen	"Almost complete type"
Two pulmonary arteries directly from truncus	Right coronary from anterior part of right sinus of Valsalva; left coronary from posterior part of left sinus of Valsalva	Not stated	Defect of the ventricular septum; foramen ovale not mentioned	"Complete" type
Small pulmonary artery branching immediately into two vessels	Coronary arteries from left posterior and right anterior sinuses	Small crista supraventricularis divides off to surround the defect in ventricular septum	Defect of the ventricular septum; right aorta with corresponding brachiocephalic distribution; closed foramen ovale, absent ductus arteriosus; pars membranacea present	Partial type
Pulmonary artery directly from truncus	Left coronary from left posterior sinus of Valsalva; right coronary from right anterior sinus of Valsalva; a typical coronary supply	Moderately hypertrophied septal muscle bundle, and very small parietal muscle bundle	Defect of the ventricular septum; right aortic arch and aorta; 4 brachiocephalic vessels; 2 pulmonary veins	"Partial" type

cases reported by Dognini (Clinica Pediatrica, 1931, p. 601) as quoted by Rizzi.[11]

TABLE I—

AUTHOR	DATE	AGE OF PATIENT	SEX	ORIGIN OF TRUNCUS	NUMBER OF CUSPS IN TRUNCUS VALVE	EXTENT OF SEPTUM AORTICOPULMONALE
Hunter and Mackey[6]	1935	Newborn	X	From right ventricle	Three cusps: 1 anterior and 2 posterior	No septum
Davison[7]	1935	14 days	X	From both ventricles, riding over the septum	Three cusps: 2 anterior and 1 posterior	A beginning of septum must be present in view of single origin of pulmonary artery
Kerwin[8]	1936	Newborn	M	From right ventricle	Three cusps: right, left, and posterior; free edges polypoid	Septum descended nearly to commissure between posterior and left cusps
Harris and Thomson[9]	1937	6 days	F	From right ventricle	Three cusps: posterior and right and left anterior; right anterior partially divided; edges thickened	No septum
Graham and Montgomery[10]	1938	5 weeks	M	Apparently from both ventricles, straddling the interventricular septum	Three fleshy cusps: apparently 2 anterior and 1 posterior	No septum
Rizzi[11]	1938	1 month	M	Both ventricles	Six large and thickened cusps	Apparently a partial septum
Kettler[12]	1939	3 months	M	Both ventricles	Three cusps: posterior and left and right anterior	Well-formed septum extending almost to the valve

CONT'D

PULMONARY BLOOD SUPPLY	CORONARY BLOOD SUPPLY	CONFIGURATION OF MUSCLE BUNDLES OF RIGHT VENTRICLE	OTHER ANOMALIES	REMARKS
Two pulmonary arteries directly from truncus	Left coronary from left posterior sinus of Valsalva; right coronary from anterior sinus of Valsalva	Not stated	Defect of ventricular septum; patent foramen ovale; sympus apus	Complete type
Pulmonary artery from truncus	Left coronary from posterior part of left anterior sinus of Valsalva; right coronary from posterior part of right anterior sinus of Valsalva	Not stated	Patent foramen ovale; defect of the ventricular septum	"Almost complete" type
Pulmonary artery from truncus	Right coronary from right sinus of Valsalva, left coronary from left sinus of Valsalva (both from posterior parts of sinuses)	Photograph shows small parietal muscle bundle	Defect of the ventricular septum; patent foramen ovale; double aortic arch	"Partial" type
Two pulmonary arteries directly from truncus	Left coronary from posterior and right coronary from left anterior	Not stated	Defect of ventricular septum; patent foramen ovale; patent ductus arteriosus	"Complete" type
Two small arteries arising from common truncus distal to great vessels; apparently bronchial arteries; no sixth arch derivatives found	Left coronary from left anterior, and right coronary from right anterior sinus of Valsalva	Not stated	Defect of interventricular septum; patent foramen ovale	"Complete" type with absence of sixth arch derivatives
Single pulmonary artery giving off two branches	Two coronary arteries; exact origin not stated	Not stated	Foramen ovale slightly open; no ductus arteriosus; defect of ventricular septum	Partial type
Truncus divided into pulmonary and aortic portions	Three coronary arteries arising from right anterior sinus of Valsalva	Photograph indicates prominent septal muscle bundle and small parietal	Defect below pars membranacea; patent foramen ovale; no ductus arteriosus; two superior venae cavae	Partial type

TABLE I—

AUTHOR	DATE	AGE OF PATIENT	SEX	ORIGIN OF TRUNCUS	NUMBER OF CUSPS IN TRUNCUS VALVE	EXTENT OF SEPTUM AORTICOPULMONALE
Goltman and Stern[28]	1939	14 months 6 days	M	From right ventricle	Three cusps: posterior right and left	No septum
						B. Possible
Motta[13]	1932	5 days	M	From right ventricle	Three cusps with vegetations; no further description	No septum
Dancourt and Bastien[14]	1935	5 months	M	From both ventricles, straddling the interventricular septum	Three cusps; no further description	None stated
Valdes Diaz and Perez de los Reyes[15]	1936	44 days	M	From left ventricle	Three cusps; no further description	None stated
Pierret and Lefebure[16]	1937	6 months	M	From both ventricles	Not stated	Not stated
Szypulski[17]	1937	8 days	M	Not clearly stated; most likely left ventricle, which here lies ventrally	Three cusps, normal	Not stated; apparently absent
Giustra and Tosti[18] (2 cases)	1939	30 and 39 hr.	M M	From single ventricle	Not stated	Partial septum in view of presence of main pulmonary artery

CONT'D

PULMONARY BLOOD SUPPLY	CORONARY BLOOD SUPPLY	CONFIGURATION OF MUSCLE BUNDLES OF RIGHT VENTRICLE	OTHER ANOMALIES	REMARKS
Right and left pulmonary arteries given off separately	Coronaries from posterior and right sinus of Valsalva	Not stated	Defects of auricular and ventricular septa; dextro position; abnormal systemic and pulmonary veins; situs inversus	"Complete" type
Cases				
Two pulmonary arteries directly from truncus	Not stated	Not stated	Defect of ventricular septum; patent foramen ovale	Coronary ostia not described; however, most likely a "complete" type
Not clearly stated	Not stated	Not stated	Defect of ventricular septum; patent ductus arteriosus; single pulmonary vein	Not sufficient information; could be truncus solitarius aorticus
Single "pulmonary" artery high from arch of aorta; more probably a bronchial artery	Not stated	Not stated	Persistent sinus venosus; absent auricular septum; defect of ventricular septum	More likely a truncus solitarius aorticus without transposition
One pulmonary artery from truncus	Not stated	Not stated	Not stated	Insufficient information
Pulmonary artery from truncus	From truncus; no further information	Not stated	Almost absent auricular septum; defect of the ventricular septum	Insufficient information
Single pulmonary trunk from truncus, which divided into two pulmonary arteries	Not stated	Not stated	Single auricle Single ventricle	Identical twins both with same type of congenital heart; most likely common truncus, "partial" type

bound on all sides by musculature. There was no membranous portion of the interventricular septum. The muscular septum itself presented no abnormality.

The septal portion of the musculature just described divided the right ventricular cavity into equally sized inflow and outflow parts. The inflow portion communicated with the right auricle through an orifice guarded by an atypical bicuspid right auriculoventricular valve. The outflow region communicated with a large artery which was the only efferent vessel emanating from the heart.

The orifice of this arterial trunk measured 3 cm. in diameter. It was guarded by a valve with three cusps: a posterior, and right and left anterior. The posterior and left anterior were large and of equal size, while the right anterior was a small cusp. Whereas the edge of the right anterior curtain was semilunar in shape, the other two valve curtains sloped towards a center peak and were therefore "tent" shaped. The peak of the tent of the left anterior cusp coincided with a longitudinal furrow which extended throughout the sinus of Valsalva, bisecting it. One coronary ostium lay above the commissure between the posterior and right anterior cusps. Within the sinus of Valsalva of the left anterior cusp immediately adjacent to the commissure between this cusp and the right anterior cusp, there was another slightly larger coronary ostium. It was thus evident that the noncoronary cusp was the right anterior which was also the small cusp. The edges and substance of the cusps were thin and smooth. The arterial trunk presented a group of low, not well-defined irregular ridges which became most prominent about the coronary ostia. One centimeter above the origin of the single arterial trunk, and at about the region of the pericardial attachment, two arteries emerged from the left posterolateral part of the common arterial trunk. These vessels proceeded to the hili of the lungs and were the pulmonary arteries. The medial edges of the mouths of these arteries obliquely faced each other and were almost confluent. Overhanging their superior margins, there was an archlike ledge. The right border of this ledge was almost straight and gave off smaller radiating ledges. The left border was rounded and concave, being continuous with a low ledge directed obliquely to the right. The brachiocephalic vessels were given off normally distal to the origin of the pulmonary arteries. Neither a ductus arteriosus nor a ligamentum arteriosum was found.

The left auricle was small and its wall was thin. It received only two pulmonary veins. (Their further course toward the lungs could not be determined.) The left auricular appendage was a relatively long narrow structure opening into the auricle proper by a fusiform-shaped mouth. The endocardium about this mouth was thickened and translucent. The left auriculoventricular valve and its orifice were small in comparison to the right but normal for the size of the left auricular and ventricular chambers. Its two leaflets and their corresponding chordae tendineae and papillary muscles presented no abnormality.

The left ventricular chamber was about one-third the size of the right. Its wall measured 0.25 cm. in thickness. The only outlet of this chamber was the defect of the interventricular septum.

The left coronary artery was connected to the ostium overlying the commissure between the right anterior and posterior sinuses of Valsalva. It extended laterally and to the left, being embedded in the wall of the truncus communis until it reached the left portion of the auriculoventricular groove. Here it gave off the anterior descending branch and continued on as the circumflex branch. In addition to forming the ramus anterior ventriculi sinistri and the ramus obtusi, it also formed the posterior descending branch. The right coronary artery was connected to the left anterior sinus of Valsalva, ran in the right portion of the auriculoventricular groove, giving off its normal branches in the anterior wall of the right ventricle. However, it terminated as the ramus marginis acuti.

DISCUSSION

The anatomic features of our case were as follows: (1) There was only one large vessel emanating from the heart, which arose from the right ventricle. This trunk gave off the coronary arteries, the systemic vessels, and two pulmonary arteries; (2) The mouth of this vessel was guarded by three semilunar cusps, a large posterior cusp, a left anterior tent-shaped cusp, and a small right anterior cusp; (3) The right and left coronary ostia lay in the sinus of Valsalva of the left anterior cusp adjacent to the right anterior cusp and above the commissure between the posterior and right anterior cusps, respectively; (4) There was an archlike ridge over the combined mouths of the pulmonary arteries; (5) There was no vessel emerging from the left ventricle; (6) There was a defect of the ventricular septum; (7) The right auriculoventricular valve had only two leaflets; (8) The foramen ovale was patent; (9) The topography of the muscle bundles of the right ventricle was abnormal.

From the first anatomic feature it is apparent that we are dealing with a truncus arteriosus communis persistens. We believe that the only criterion necessary for such a diagnosis is the presence of only one large trunk emanating from the heart which gives off the coronary arteries, the pulmonary arteries, and the systemic arteries. This differentiates the condition from truncus solitarius pulmonalis and truncus solitarius aorticus, where a vestige of the atretic vessel is found, thus pointing to a previous division of the truncus.

The number of semilunar valves is not a primary criterion for the diagnosis. Of course, where there are four cusps, the embryonic condition is retained. But in many cases there is a malformation in the cusps, at times compensatory, so that only three are present (sometimes with a rudimentary fourth), while in the case of Carr, Goodale, and Rockwell,[3] two cusps were present, and in the case of Rizzi,[11] six. In our case, there were three cusps, two large and one small. It is apparent that the posterior cusp originated from embryonic bulbar cushion 1 and possibly part of 2, and the left anterior from cushion 3 and possibly part of 2. It is also apparent that the right anterior cusp was derived from cushion 4, and therefore was homologous with the normal posterior aortic cusp, the noncoronary cusp.

In view of the fact that there was an arched ledge over the combined mouths of the two pulmonary arteries, the anomaly was not of the complete type. However, it may be termed "almost complete" as the arched ledge was the only vestige of the aorticopulmonary septum.

The origin of the truncus from the right ventricle, the position of the coronary ostia, and the topography of the muscle bundles of the right ventricle show that in addition to a truncus communis we are dealing with a type of transposition. The origin of the truncus implies that

both the aorta and the pulmonary artery arise from the right ventricle. Therefore, this constitutes an incomplete transposition, or type C in our classification,[19] or type II of Spitzer.[20] The position of the coronary ostia and the noncoronary cusp showed a clockwise (looking truncusward from the ventricle) displacement of about 90°. This approximates Case 3 of our series of transpositions,[19] in which both the aorta and the pulmonary artery arose from the right ventricle.

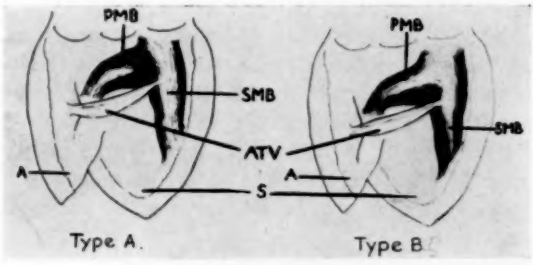

Fig. 2.—Normal topography of the muscle bundles of the right ventricle. Type A: Two distinct muscle bundles are noted. Type B: An arch of musculature is present at the base of the pulmonic valve. *SMB*, Septal muscle bundle; *PMB*, parietal muscle bundle; *ATV*, anterior tricuspid leaflet; *A*, anterior wall of the right ventricle; *S*, septal wall of the right ventricle.

The topography of the muscle bundles of the right ventricle likewise closely resembles that seen in Case 3 of our previous report.[19] In this communication we presented a study of the normal topography of the muscle bundles of the right ventricle, and of the abnormal topography in transposition. We showed that the so-called crista supraventricularis may be subdivided into a septal muscle bundle and a parietal muscle bundle with different embryological origins (Fig. 2). The septal muscle bundle originates from ridge A (Spitzer,[20] Fuchs,[21] Beninghoff,[22] Tandler,[23] and Keith[24]), while the parietal muscle bundle originates from ridge *3B*, the bulboauricular spur, and the auxiliary ridge of the ventricular septum (Keith,[24] Pernkopf and Wirtinger[25]). The parietal muscle bundle is present in mammals but not in reptiles and is related to the growth of ridge *3B*, while the septal muscle bundle is very well developed in the reptile and is less developed in the mammal. In certain types of transposition (tetralogy of Fallot, transposition with tricuspid atresia, transposition with aneurysm of the membranous septum), the parietal muscle bundle is either smaller than normal or absent, while the septal muscle bundle is hypertrophied (Spitzer,[18] Humphreys,[1] Saphir and Lev[26]). This abnormal muscle configuration was present in Humphreys' case of truncus communis and is also seen in the cases of Beaver,[2] Kettler,[12] Bredt,[4] and of Roos.[5] In our case we found a modification of this type of topography but essentially the same configuration. There is an arch of musculature at the base of the ventricle which forms the inferior border of the interventricular foramen. This

arch is really the main limb and inferior arm of an obliquely formed Y-shaped structure, the upper arm of which is fused with the ventricular septum. Thus, the parietal and septal muscle bundles are fused. But it is apparent that the parietal muscle bundle component is small, while the septal muscle bundle component is relatively large. The small muscle bundle passing through the defect into the left ventricle we consider to be the bulboauricular spur which had not atrophied. Thus, the topography of the muscle bundles resembles that seen in type C (partial) transposition.

We have indicated elsewhere our conception of transposition.[26, 27] Briefly it indicates an abnormality in the second phase of the development of the heart, an abnormality in the absorption of the bulbus. Normally during the second phase, 150° torsion occurs at the distal bulbar ostium (counterclockwise looking truncusward from the bulbus), and 45° backtorsion (clockwise looking bulbusward from the ventricle) at the proximal bulbar ostium, accompanied by ventral deviation of the bulbus[25] (Fig. 3). In transposition we believe there is an abnormality in the formation of mammalian bulbar ridge *3B* (a recent phylogenetic development). It is either absent, decreased in extent, or has the direction of one or the other of its reptilian forebears, ridge *4B* or *3C*. The absorption of a bulbus containing such an abnormal ridge proceeds abnormally, resulting in less or excentric torsion at the distal ostium, and excentric backtorsion at the proximal ostium.

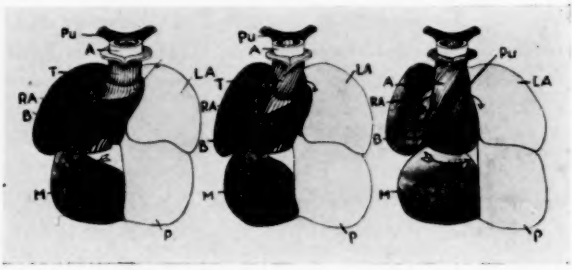

Fig. 3.—Second phase of the development of the heart. The absorption of the bulbus. *LA*, Left auricle; *RA*, right auricle; *P*, proampule; *M*, metaampule; *B*, bulbus; *T*, truncus; *Pu*, pulmonary artery; *A*, aorta. (From Pernkopf and Wirtinger.)

In our case, the coronary ostia were displaced 90°. This means that instead of the normal 150° torsion occurring about the center of ostium bulbotruncare during the absorption of the bulbus, only 60° torsion must have occurred (Fig. 4, *III* and *IV*). This lessened torsion we assume to be due to the abnormally small ridge *3B*, or ridge *3B* is completely absent, or it is replaced by ridge *3C*, with a lesser twist than the normal ridge *3B*. In the process of unwinding of the unequally twisted ridges (resulting in torsion at ostium bulbotruncare), less torsion occurred at

the distal ostium. Also the unwinding did not occur about the center, but rather about a point between the center and cushion 1 (Fig. 4, *III*), or about cushion 1 (Fig. 4, *IV*). In the proximal ostium likewise backtorsion did not occur around the center of the bulbus as an axis but rather around a point between the center and cushion A (Fig. 4, *IX*), or about cushion A (Fig. 4, *X*). This threw the aortic portion of the bulbus partially or completely into the right ventricle. Thus there ensued a partial transposition (both aorta and pulmonary artery emerging from the right ventricle).

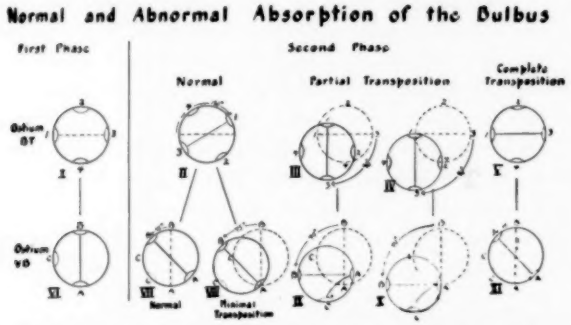

Fig. 4.—Absorption of the bulbus in transposition. There is an abnormality in the formation of ridge *3B* whereby it is poorly formed or replaced by ridge *4B* or *3C*. This results in decreased torsion at the distal ostium. In addition, this torsion occurs either around cushion 1 as a center or close to cushion 1. At the proximal ostium, backtorsion occurs around cushion A as center or close to cushion A. This backtorsion may be 45° or may be 90°, as is normally present in an earlier stage.

1, *2*, *3*, and *4*, Distal bulbar cushions; *A*, *B*, *C*, proximal bulbar cushions; *BT*, bulbotruncare; *VB*, ventriculobulbare; *I*, *VI*, distal and proximal bulbar ostia, respectively, at the end of the first phase (normal and in transposition); *II*, *VII*, distal and proximal bulbar ostia during the second phase in normal absorption of the bulbus; *II*, *VIII*, bulbar ostia in transposition with congenital aneurysm of the membranous septum during the absorption of the bulbus; *III*, *IX*, bulbar ostia in partial transposition during the absorption of the bulbus, where torsions occur close to cushions 1 and A as centers; *IV*, *X*, bulbar ostia in partial transposition during the absorption of the bulbus, where torsions occur about cushions 1 and A as centers; *V*, *XI*, bulbar ostia in complete transposition where no torsion occurs at the distal ostium while mild backtorsion occurs at the proximal ostium.

The lack of division of the truncus into the aorta and pulmonary artery in our present anomaly is due to the inhibition in the formation of the septum aorticopulmonale trunci. In other words the spurs between the fourth and sixth branchial arches, although they fused in our case, did not proceed downward to form the septum aorticopulmonale trunci. This may be correlated with the abnormal ridge formation in the bulbus. In other words there has been a combined lack of formation of the septum aorticopulmonale trunci and ridge 3*B*. This takes on added interest when we recall that most if not all cases of truncus communis are accompanied by transposition. In other words where the septum aorticopulmonale has not formed there is usually, as we believe, a concomitant abnormality in ridge 3*B*.

The defect of the ventricular septum is explained as in all cases of transposition on the basis of lack of complete formation of ridge *3B*.

The small parietal muscle bundle is likewise explained on the basis of the poor development of ridge *3B*, of which, in part, it may be considered a continuation.

The muscle bundle passing from the base of the truncus into the left ventricle is interpreted by us as a persistent bulboauricular spur. Since the atrophy of the left portion of the bulboauricular spur is dependent upon the absorption of the bulbus, it is apparent that when this absorption has not proceeded regularly the bulboauricular spur may remain definitely in its muscular form.

There remains to be explained the bicuspid right auriculoventricular ("tricuspid") valve in our case. That this is not the mitral valve can be ascertained from the topography of the attached papillary muscles. There is the normal ventrolateral papillary muscle attached to the large anterior leaflet and a normal papillary muscle of Lancisi. Thus the anterior leaflet, although enlarged, is the normal anterior leaflet of the tricuspid valve. The medial leaflet, however, although possessing its usual direct chordal attachment to the septum, is attached to an oblique papillary muscle which arises from the inferior (posterior) wall of the right ventricle. From the point of view of its origin, this is the posterior papillary muscle. However, it is not attached to the posterior leaflet, which is apparently fused with the medial leaflet.

The explanation of this may be found in the fact that the process of absorption of the bulbus occurs earlier in fetal life than the formation of valves. Therefore, at the time of the formation of valves, the presence of the large truncus in the right ventricle created inflow and outflow areas of the right ventricle which met each other at a very acute angle. (The normal angle between inflow and outflow portions of the right ventricle is about 70°.) This created current relationships similar to those found at the mitral valve. (Normally the angle between the inflow and outflow portions of the left ventricle is very acute.) Thus, there was the tendency to form two instead of three leaflets and the abnormal attachment of the posterior papillary muscle (now parallel to the current) in an oblique direction to the medial leaflet.

SUMMARY

A case of truncus arteriosus communis persistens is presented with a review of the literature since 1932 (Humphreys' review covers the cases reported up to 1932). A phylogenetic and embryologic explanation of the anomaly is offered. Most cases of truncus arteriosus communis persistens may be explained as mild to moderate degrees of transposition, where there is a combined abnormality in the bulbar ridge *3B* and the septum aorticopulmonale trunci. The abnormality in ridge *3B* produces an abnormality in the absorption of the bulbus resulting in transposition.

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MERCURY POISONING FROM TOPICAL APPLICATION OF FIFTEEN PER CENT AMMONIATED MERCURY

Report of a Case

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THE case reported here is of interest because of the large amount of mercury absorbed through the skin subsequent to the application of an ointment of 15 per cent ammoniated mercury, and because the poisoning manifested itself as a generalized exfoliative dermatitis rather than as renal damage. In 1934, when Harper[1] reported two cases of generalized rash and stomatitis following the use of 10 per cent ammoniated mercury, he was able to find, in the literature, reports of only five cases of poisoning from local application of the drug. This case is probably the eighth one to be reported.

The degree of absorption of mercury through the skin was determined by quantitative tests of the mercury in the urine, which yielded results as high as 4 mg. per liter. In spite of this high concentration of mercury in the urine, signs and symptoms of renal damage were absent and laboratory tests of kidney function were normal.

CASE REPORT

A white girl, 18 months of age, was admitted to the Children's Hospital on Jan. 9, 1941, because of skin trouble and draining ears. The history given by her parents was that she had had earache and drainage of pus from the right ear for a month, with a swelling beneath the ear beginning shortly after the start of her trouble. At the time of admission the left ear had been discharging pus for three days. Six days after the original ear trouble began a rash developed around the right ear. An ointment of 15 per cent ammoniated mercury was applied daily, but after a week's time the rash had spread considerably, and a generalized reddening of the skin gradually developed. The family continued to apply the ointment to all of the abnormal skin areas until about ten days before admission. By that time a generalized scaling and crusting of the skin were present, along with severe pruritus. The parents then began to suspect that the ointment was too strong, so they diluted it with an equal part of lard and continued to apply the half-strength ointment (7.5 per cent ammoniated mercury). For a few days before coming to the hospital the child had been drooling a great deal. There was no history of exposure to scarlet fever.

Physical Examination.—Upon admission the patient was poorly developed and nourished and was continually scratching various portions of her body. The rectal temperature was 99° F. Patches of dead epidermis were observed over most of the body, and these continued to fall off in large flakes during the examination. Moisture was excessive in the folds of the skin. There were no crusts, vesicles, or pustules

From the Children's Hospital Research Foundation and the Department of Pediatrics, College of Medicine of the University of Cincinnati.

Quantitative analyses of mercury in the urine were done by the Kettering Laboratory of Applied Physiology, Cincinnati.

present. The lips were cracked and fissured and showed evidence of recent bleeding. Salivation appeared somewhat excessive. The skin over the buttocks was fissured and covered with scales. Beneath the scales the skin was rough and indurated, and there was erythema around the genitals and in the antecubital areas. The hands and feet were moderately edematous and bluish in color. There was some edema of

Fig. 1.

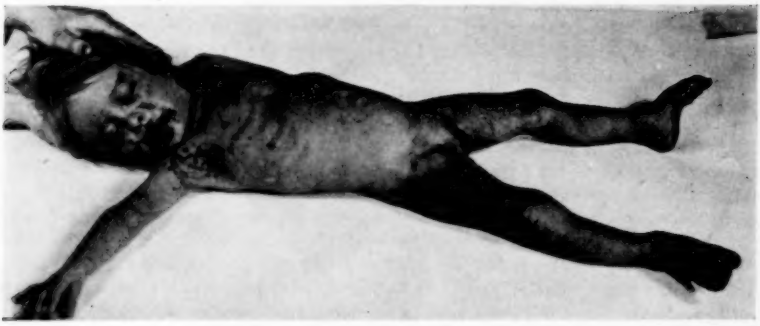

Fig. 2.

Figs. 1 and 2.—Nature and distribution of the eruption on Jan. 16, 1941.

the face and moderate scaling of the scalp. The hair was coarse and dry. There was thick, white pus in both ear canals. The tympanic membranes presented a beefy appearance. There was no palpable lymphadenopathy except beneath the right ear. The mucous membranes of the mouth, throat, and tongue were normal.

Figs. 1 and 2 were taken a week after admission when, after daily baths with sulfonated oil, most of the desquamation had disappeared.

Laboratory.—Culture of the throat secretions contained a few hemolytic streptococci. The blood examination on admission showed: Hemoglobin, 10.8 mg. per 100 c.c.; red blood cells, 4,580,000 per cubic millimeter; white blood cells, 35,750 per cubic millimeter; polymorphonuclear cells, 49 per cent; lymphocytes, 20 per cent; eosinophiles, 15 per cent; monocytes, 16 per cent. The urine occasionally contained a trace of albumin. The blood pressure averaged about 90/60. Blood urea nitrogen, 16.7 mg. per 100 c.c.; blood creatinine, 1.5 mg. per 100 c.c. The Dick test was negative. Culture of the purulent material draining from the ear revealed hemolytic staphylococcus aureus and nonhemolytic streptococcus.

On January 14, five days after admission, a specimen of urine analyzed by D. M. Hubbard of the Kettering Laboratory of Applied Physiology, using a method recently described,[2] was found to contain 0.2 mg. of mercury in 50 c.c., or 4 mg. per liter of urine, an amazingly high concentration.

Course in Hospital.—Besides the daily bath with sulfonated oil, elixir of phenobarbital and nembutal were administered to relieve itching. Quinolor ointment was applied to the indurated auricles and boric acid ointment to the cracked lips. Various vitamin preparations were given in large amounts, including riboflavin and nicotinic acid. The scaling of the skin disappeared within a week after treatment was started, and during this time there was slight elevation of temperature, but the rough, thickened appearance of the skin, and the erythema and the fissures were not completely gone until six weeks later (February 26). During the last ten days of February, an ointment of 1 per cent copper sulfate was applied to the areas on the face which were still affected.

Both ears drained most of the time during the patient's stay in the hospital. Sulfathiazole (1.5 gr. per pound of body weight) was administered daily from January 15 to January 23 without visible effect on the purulent discharge from the ears. On January 30 a Bezold's abscess developed on the right, and the following day a right mastoidectomy was performed with drainage of the abscess. Three days after operation there developed a purulent conjunctivitis of the right eye which cleared in fifteen days with the administration of zinc and boric solution. Both ears continued to drain profusely and sulfanilamide was given (1 gr. per pound of body weight per day) from February 4 to February 12 without any effect on the discharge. X-ray therapy was used to help reduce the swelling on the right side of the neck. On March 8 the tonsils and adenoids were removed. On April 1 a left mastoidectomy was performed. As the ears still continued to discharge, on April 25 a more radical left mastoidectomy was performed. Cultures from both mastoids at operation revealed hemolytic streptococci. Cultures from both ears were negative for diphtheria bacilli. The child gained weight rapidly during this period and was in excellent health although her ears still continued to drain. Finally, on May 16, sulfathiazole was again administered and within a week the drainage from the ears had ceased. Sulfathiazole was stopped on May 30 and the patient was discharged two days later.

On March 7 a specimen of urine was found to contain 0.06 mg. of mercury per liter. The concentration of sulfanilamide in the blood rose to 3.4 mg. per 100 c.c. of the free drug and 2.3 mg. per 100 c.c. of the conjugated drug. Blood sulfathiazole levels rose to as high as 4.5 mg. per 100 c.c. of the free drug and 2.4 mg. per 100 c.c. of the conjugated drug. The patient was given one transfusion during her stay in the hospital.

DISCUSSION

In most cases systemic absorption of mercury is apt to manifest its toxicity mainly by causing damage to the kidneys.[3-5] The high concentration of mercury in the urine in this case indicated the absorption

of large amounts of mercury from the 15 per cent ammoniated mercury applied to the skin. Yet, in spite of the excessively high amount of mercury in the urine, there appeared to be no renal damage so far as could be ascertained from symptoms, urinalyses, and blood chemistry. The poisonous effects appeared to be limited mainly to the skin, even to many areas to which the ointment had not been applied.

Ointment of ammoniated mercury is widely used in the treatment of various dermatoses. While adults seem to tolerate concentrations of 10 per cent or more without the development of symptoms of intoxication, it is probable that stronger percentages can cause toxic manifestations in children, especially if continued for a period of many days. In this case an ointment of 15 per cent ammoniated mercury was used for a total period of four weeks. During the last ten days of this period the concentration was somewhat uncertain because of dilution with lard. The absorption may have been somewhat greater than usual in this case, but the danger of mercury poisoning must be considered whenever this preparation is used, especially in children.

SUMMARY

A case of mercury poisoning is reported, caused by the daily application of an ointment of 15 per cent ammoniated mercury to skin areas for three weeks, followed by use of the same ointment diluted in equal portions with lard for a period of ten days.

A concentration of 4 mg. of mercury per liter was found in the urine.

The poisoning affected mainly the skin, causing a generalized exfoliative dermatitis. There were also some stomatitis and moderate edema and cyanosis of the hands and feet.

There appeared to be no renal damage in the case here reported.

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FEEDING BEHAVIOR OF AN INFANT DURING THE FIRST TWELVE WEEKS OF LIFE ON A SELF-DEMAND SCHEDULE

A Narrative by the Mother With Discussion by the Pediatrician

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"Fresh air, sunshine, adequate clothing, food and sleep are among the approved satisfactions which are conscientiously provided and are a part of our program for nursery care. But there are other needs which any thoughtful observer must come to recognize as equally important. The warmth and contact of the mother in the first few weeks, the security of fondling, freedom from physical restraint, permission to eat, sleep, and eliminate according to his own individual rhythms rather than by those imposed by arbitrary regimes, the opportunity to try out and use his emerging activities as they appear within the developmental plan, these also may be considered as positive requirements. In other words, the gratification which the baby gets from the fulfillment of these needs is the spark which makes the developmental plan work at its maximum efficiency. It is back here, in the comparatively simple performance of the earliest days of life, that the child begins to develop the positive conditioning and the sense of competency which we recognize as so important for the later success of the individual."—Aldrich, C. Anderson: J. Pediat. 15: 578, 1939.

INTRODUCTION

Narrative.—This record of the feeding behavior of an infant on a self-demand schedule has been made by the infant's mother, utilizing many of the techniques of Gesell and Ilg.[1] Their records do not include the first days of life of the infants. In this instance it was possible to begin the study on the first day and to carry it on continuously. The records were kept by the mother as the incidents occurred.

The study was made incidental to a feeding program that was considered optimum for the baby's welfare. The baby, although delivered in a hospital, was kept in the room with the mother‡ because of the conviction of the pediatrician and the mother that a baby during the first days of life needs the loving, personalized care of the mother, that he needs during these first days to be placed at the breast when he is awake and indicates a readiness to nurse, that the mother, if she so desires, is entitled to the pleasure of this intimate contact with her baby and the opportunity which it affords for continuous observation of his growth and development from the first day.

Discussion.—To observe the "natural" behavior of an infant during the first few weeks of life has been enlightening. Neither mothers nor

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‡This arrangement was possible through the courtesy of George Washington University Hospital, Washington, D. C., and the cooperation of the obstetrician, Dr. Howard W. Kane.

obstetricians readily accede to a similar program. All recent investigations have been concentrated on physical improvements in obstetric and nursery care. Lower morbidity and mortality rates have resulted, but this improved physical technique has played havoc with the emotional adjustment of mother and infant, and successful breast feeding.

FEEDING INTERVALS

Narrative.—Twenty-four hour cycles of day and night have no relationship during the early days of life to the baby's spontaneous demands for food. Hence the following discussion of these demands in terms of twenty-four cycles gives an arbitrary picture; yet, in view of the fact that the infant will eventually adjust to such a cycle, it is the realistic approach.

Chart 1 plots the sleeping and the feeding intervals of the infant during the first two weeks of life. The infant was offered the breast, nursing for ten minutes when he was about 4 hours old. About four hours later he cried and was again placed at the breast, nursing for twelve minutes. The infant was awakened for the two subsequent feedings in order to stimulate the flow of milk. All of the following feedings were given on the demand of the infant with a few rare exceptions. The infant's total of fifty-four feedings during the first week of life, ascending from three feedings on the first day to eleven feedings on the fifth day,* contrasts with the six-feeding day usually planned. From the sixth day to the fourteenth day his demands varied from six to nine feedings daily as shown on Chart 1.[2]

During the third week of life the infant had five six-feeding days and two seven-feeding days. The fourth week the infant was more variable, one day demanding five feedings, four days, six feedings, and on two days, seven feedings. During the fifth week the infant demanded only five feedings on five days of the week. During the sixth week the infant responded to an inadequacy in the mother's supply of breast milk by increasing to six, seven, and eight daily feedings. Complementary feedings were then offered. These feedings were not readily accepted and were discontinued after eight days. The total complementary intake was 16 ounces. During the seventh and eighth weeks the baby returned to a five-feeding schedule. On four days of the ninth week the infant demanded only four feedings, sleeping for continuous periods of twelve and thirteen hours on these days. This reduced number of feedings lessened the average daily intake, slowing down the rate in weight gain; hence it was decided to awaken the baby if necessary for the fifth feeding. Thus throughout the tenth, eleventh, and twelfth weeks the infant followed a five-feeding schedule. Beginning with the sixty-eighth day the practice was initiated of awakening the baby for a bedtime feeding. This eliminated the feeding which the infant had

*The day of birth is considered the first day of life for the purposes of this study.

previously been demanding at the inconveniently early hours of 2 to 4 A.M. From this point the infant was also occasionally awakened for the fourth feeding if he did not spontaneously awaken within four to five hours of the third feeding.

Discussion.—The young of every animal nurses its mother soon after birth. The human infant, having to be carried to its mother, is delayed for a longer period at the whim of the adult. Among less "civilized" peoples this interval depends on the "labor recovery" of the mother. If no abnormal condition exists, the infant will nurse. Probably up to this moment of first nursing no "hunger tension" has occurred to demand gratification. In the present instance the infant had shown no "rooting," "sucking," "crying," or other manifestations of hunger before he was offered the breast. But his reaction was prompt and nursing was accomplished successfully. Moving the head from side to side and arm movements were active when the nipple was "lost," indicating an appreciation of this first contact. As stated, he awakened four hours later, nursed all of twelve minutes and was satisfied. The gratification of this first demand of "hunger tension" was followed by a long period of quiet. In fact he was awakened at the next two four-hour intervals to stimulate the secretion of milk. Perhaps this was an error in that we interfered with what might have been prolonged sleep.

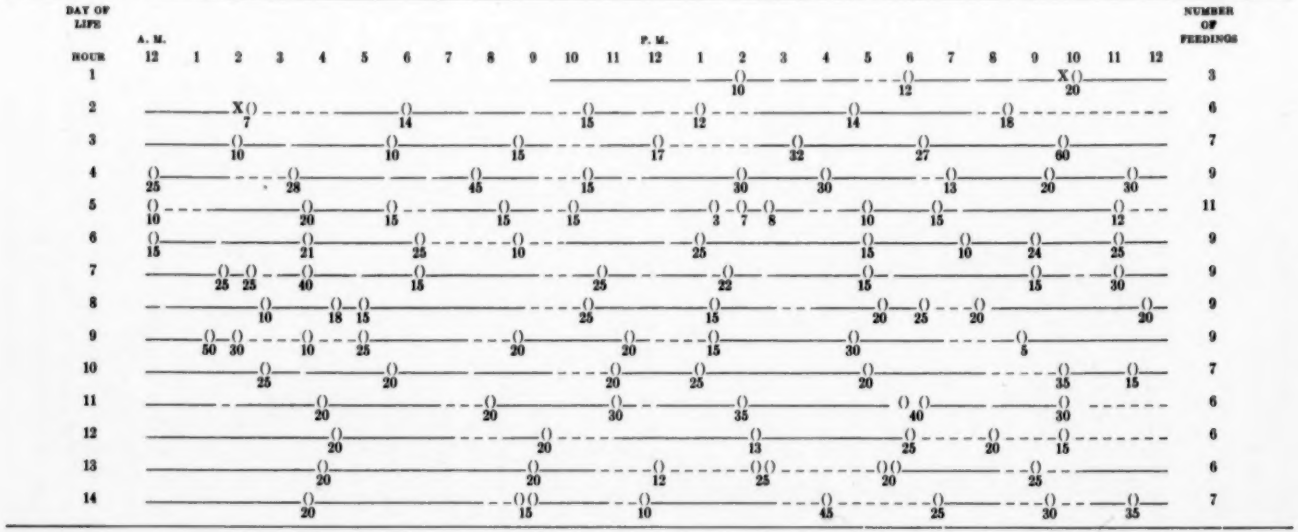
The nursings during this first week were easily accomplished, the infant "taking hold" with alacrity, this in contrast with so many infants who must be "coaxed" and "prodded" by all the methods known to modern nursery technique. It is not necessary that an infant be "taught" to nurse if hunger is allowed to develop and not dulled by early complementary feedings. This infant was given only plain water three to four times a day and this was offered first seventeen hours after birth. His first nursing experience comprised contact with the mother. This contact brought to him the first gratification of hunger tension. Would it seem illogical to assume that this "gratification" far surpassed that derived from the usual bottle?

FEEDING CHARACTERISTICS

Narrative.—Characteristic of the infant's spontaneous demand for food was the tendency during the first weeks of life to prolong a feeding, as, for example, on the third day when he nursed for sixty minutes, or to demand several feedings at short intervals, as on the fifth day. As shown on Chart 1, this demand for frequent feedings reappeared during the early morning hours on the seventh, eighth, and ninth days and then did not reappear in comparable degree. From this period the tendency was toward a consistent number of daily feedings as indicated by the chart. Longer periods of sleep began to appear about this same time. By the ninth week the infant was sleeping for periods of twelve hours.

Chart 1

First Fourteen Days

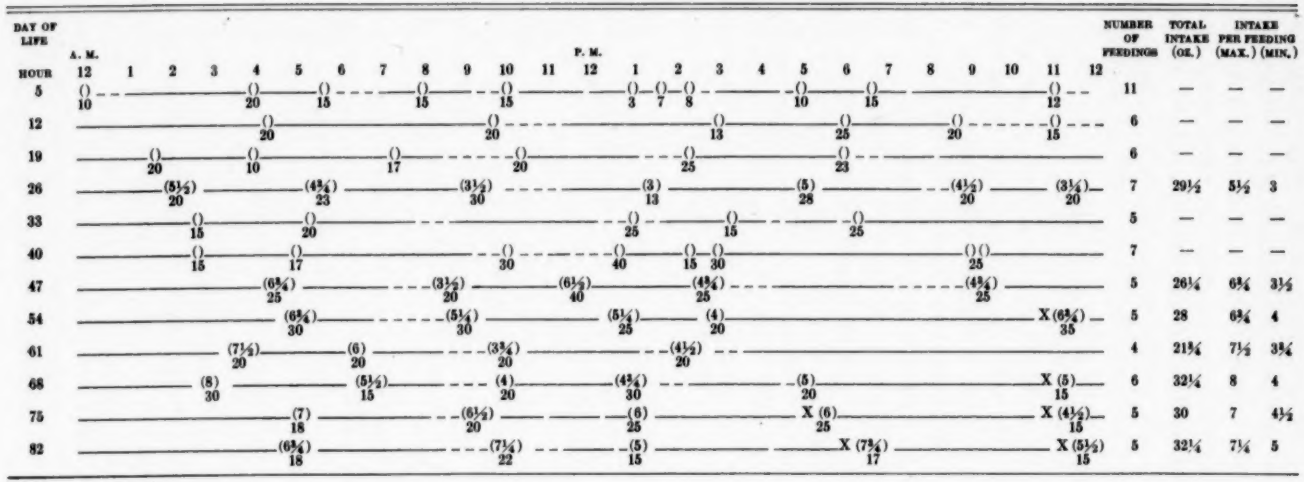


Key: _____ Sleep
- - - - - - Awake
() Feeding Period

Figures below () nursing time in minutes
Figures in () number of ounces per feeding
X() Awakened for feeding

Chart 2

Successive Tuesdays, First Twelve Weeks



Key: _____ Sleep
- - - - - - Awake
() Feeding Period

Figures below () nursing time in minutes
Figures in () number of ounces per feeding
X () Awakened for feeding

However, the practice initiated on the sixty-eighth day of awakening the infant for a late feeding eliminated this tendency, serving to space the feedings more evenly. While eliminating the demand for an early morning feeding, the infant continued to awaken and demand a feeding five to seven hours after the late feeding. He did not on any occasion spontaneously awaken for this late feeding and slept most of the time while nursing. The intake for the feeding was average, however.

FEEDING TIME

Narrative.—The infant was allowed to remain at the breast for each feeding until he indicated satiety. Records were made of the time that he required, the number of minutes being noted on the charts. During the early weeks the infant slept considerably while at the breast, but as he grew older he tended to reduce the time required for feeding and to become more consistent. At times during the early weeks the infant seemed unable to stay awake long enough to complete a feeding, as on the fifth, seventh, and ninth days. In contrast, the infant during the eleventh and twelfth weeks at some feedings nursed rapidly, often taking the major portion of his intake in six to eight minutes, then prolonging the nursing five to ten minutes with playful nursing and cooing, at other feedings, particularly the late feeding, tending to revert to the early pattern of relaxed, sleepy nursing.

Discussion.—This infant was not regular in the periods of time spent in feeding at the breast, becoming satisfied in many instances in five to ten minutes. At other times his nursing period was prolonged without increasing the quantity of milk taken. This has been observed on many occasions both in breast-fed and bottle-fed babies. There is a group of infants who require a long period of nursing for gratification, even though most of the milk is obtained in the first few minutes. Permitting the infant thus to prolong the nursing, I believe to be conducive to the development of a "good" baby. If these babies are removed from the breast when a specified amount is taken, or when the bottle is empty of its contents, they will continue to mouth, suck their finger, and give other indications of lack of contentment. The usual twenty-minute nursing period stipulated by dogmatic nursery technique has no place in the development of this pattern of contentment.

FOOD INTAKE

Narrative.—Food intake was first computed on the sixteenth and seventeenth days of life. On the sixteenth day the total intake was 22 ounces in seven feedings, with a maximum intake at any one feeding of four ounces and a minimum of two. On the seventeenth day the intake was 26½ ounces, with intake in a specified feeding varying from 2 to 6 ounces. On the twenty-fifth day the intake was 25 ounces, with a

range of intake from 3 to 5¾ ounces. The twenty-sixth day the intake was 29½ ounces, ranging from 3 to 5½ ounces. Table I shows the daily intake as it is averaged for each week beginning with the fifth, together with the minimum and maximum intake on any given day. No specific feeding during the twenty-four-hour cycle was characterized by a consistently larger intake.

Discussion.—This infant's feeding behavior shows a lack of consistency in the amounts of food taken with complete gratification evidenced with small as well as large intakes. Such wide variations as 3 and 6 ounces are noted as early as the sixteenth day of life. This pattern contrasts sharply with our modern routine of prescribing an accurate number of ounces for each individual feeding. Experience is piling up evidence against this stereotyped practice, much to the joy of the infants concerned.

TABLE I

WEEK OF LIFE	WEIGHT GAIN (OUNCES)	TOTAL NUMBER OF FEEDINGS	AV. DAILY INTAKE* (OUNCES)	DAILY INTAKE	
				MIN. (OUNCES)	MAX. (OUNCES)
1	4	54	--	--	--
2	4	50	--	--	--
3	11½	44	--	--	--
4	6½	43	--	--	--
5	6½	38	23.7	23	25½
6	10½	44	27.4	21½	28½
7	6	36	28.3	26¾	36¼
8	7½	36	28.1	26½	31
9	3½	31	25.0	21¾	28¾
10	8	36	28.4	26	32¼
11	7¾	35	29.7	28½	30¾
12	6¼	35	30.4	28½	33

*The averages for the fifth week are based on records taken on four days, for the sixth week, on the basis of records of five days. All of the subsequent averages are based on records taken on seven days of the week.

WEIGHT

Narrative.—Because of the premium placed upon breast feeding by those responsible for the infant, it was agreed that supplementary bottle feedings would be postponed following birth until the infant's welfare made such feedings imperative. Weight loss following birth was greater than usual. The rate of weight gain throughout the twelve weeks under consideration was slower than average. The infant weighed 9 pounds and 10 ounces at birth, losing to 8 pounds, 12 ounces on the third day. The birth weight was not regained until the nineteenth day. This slow rate of gain is interesting considered in the light of the infant's consistently good physical condition, his tendency to be a good sleeper, and his readiness to adjust to a five-feeding day.

Discussion.—A great mass of literature has appeared concerning initial weight loss, its significance, prevention, and the means of accelerating the return to birth weight. In this infant the initial weight

loss was greater than that usually encountered and the return to birth weight was slower. Dehydration temperature did not occur. It is probable that had we used a complementary feeding or sugar solution in place of plain water, the return to birth weight would have been more rapid. Since no physical disturbances occurred, I feel that we were justified in the procedure followed. This schedule might not be so easily maintained with parents who feel unduly concerned about initial weight loss. Confidence in the physician responsible for the baby's welfare would determine a modification in a similar experience.

SLEEP

Narrative.—As the charts indicate, the infant was a consistently good sleeper. The periods of wakefulness, although somewhat variable, occurred most consistently between the early and late morning feedings. In some instances these periods of wakefulness were broken by a short nap. During the latter part of the twelve weeks under consideration, the period of late afternoon wakefulness developed. As Chart 3 shows, this period of wakefulness influenced the hour of the fourth feeding, making it more irregular than the other feedings.

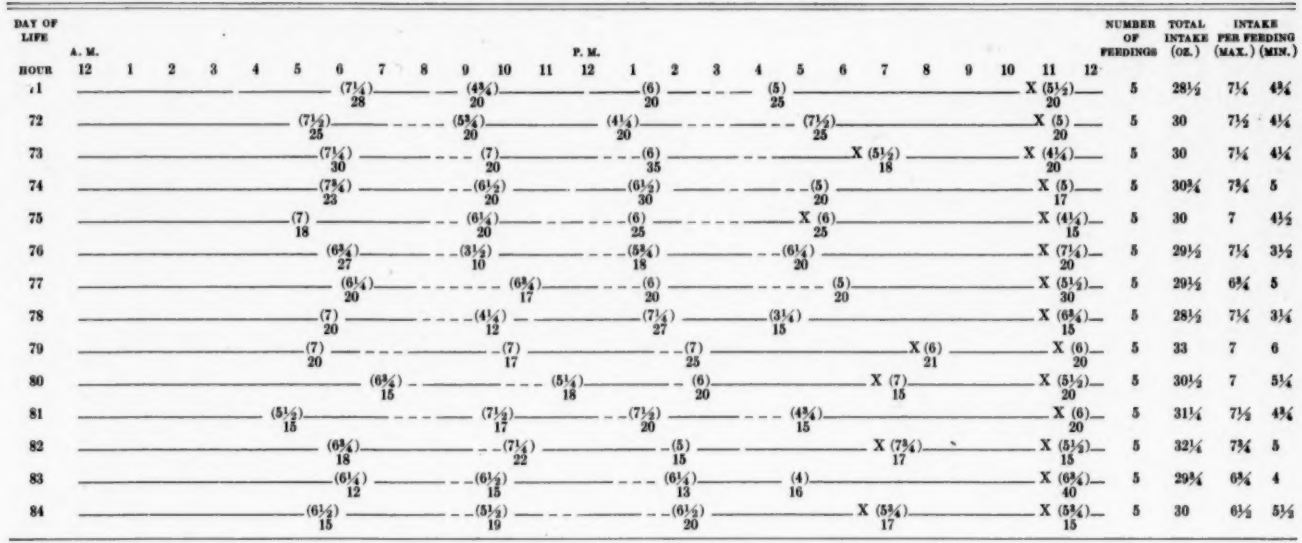
SUMMARY

Narrative.—In summary it can be said that during the first nine to ten days of life the infant demanded more feedings and spent more time in nursing than is permitted to a baby who spends these early days in a hospital nursery. Aside from this early period, the infant's spontaneous demands, although highly variable, conformed roughly to the six- and later five-feeding day usually planned for infants. The infant did not respond to the program of indulgence by making excessive demands, but on the contrary slept well. Toward the end of the first ten-week period, the infant's feeding intervals became more regular. From the tenth through the twelfth week, as Chart 3 shows, the program was one of essential regularity with only minor, but none the less significant, variations influenced by the hour of awakening and the length of the morning nap. In short, with only the external influence of being awakened for the late feeding, this infant in less than twelve weeks adjusted himself easily and comfortably to the routines of his environment.

Raising a baby on this simple and ancient program of feeding him when hungry, such as has been done in this instance, although it is receiving increasing recognition as a foundation stone of mental hygiene during infancy, is foreign to our clock-ruled society. At this time when the four-hour feeding schedule is conventional the mother who employs primitive methods encounters some of the difficulties involved in doing the unusual. Her guide becomes not the clock but the baby's behavior. Weinfeld[3] has pointed out that in some instances these factors may tend

Chart 3

Eleventh and Twelfth Weeks of Life



Key: _____ Sleep
_ _ _ _ _ Awake
() Feeding Period

Figures below () nursing time in minutes
Figures in () number of ounces per feeding
X() Awakened for feeding

to foster rather than eliminate anxiety by unduly upsetting family routine. Shifts which were made in family routine in this instance were few and unimportant and carried out without resulting confusion. Close supervision from the pediatrician during this early period is important. If the experiences of this mother have any wide applicability, other mothers could gain comfort and satisfaction from a simple and natural program of infant feeding similar to the one which has been described.

Discussion.—The objective in the program for this infant was gratification of the physical and emotional needs as they arose. Pediatricians recognize that a newborn infant has both a physical and a mental development to understand. In the case of this infant, early contact was made with the mother to acquaint him with his natural source of hunger gratification as well as the early establishment of the mother-infant unity. Breast feeding was established in accordance with animal behavior as well as that of primitive peoples. It was not necessary to "teach" this infant to nurse. No restrictions were placed in the way of the first expressions of development. Initial weight loss was rightfully considered as physiologic, hence not combated with the usual complementary solutions.

The usual disturbance occasioned by the arrival home of the new baby was absent, the mother had watched the "early emerging activities" and heard the "pug-dog grunts and breathing noises" as they occurred. With nursery-managed babies the mother has had practically no opportunity to observe, in the first few days, the awakening and development of her baby's personality. As time goes on, the baby attempts more vigorously to make his wishes known. Thus when the baby reaches home, the mother is suddenly confronted by an active, alert, and demanding infant quite different from the pictured ideal of the newborn. Small wonder she is unprepared to evaluate his demands. Up to this time the infant has been on a "command" schedule having no consideration for his own rhythmic hunger awakening. Despite the twelve days of nursery "training," the baby still demands his feeding when hungry. In this instance the feeding intervals and time spent in nursing depended entirely on the infant's desires until the ninth week, when the late evening feeding was introduced to fit more conveniently into the household routine. Routine and schedules are desirable in most households, and present-day mothers have been thoroughly educated to this idea. The education of an infant to this plan should take into consideration the fact that infants will establish such a schedule. If the infant is slowly initiated into waiting for gratification of his hunger tension, the base of the schedule hour becomes appreciably narrowed without effort. In this way, long crying periods because of hunger and the forcing of unwanted food are both avoided. There is no more potent cause for

anorexia and other feeding behavior problems than this strict compliance to "time command" schedules.

In my opinion, the freedom from conventional regime, as outlined in the above narrative, established a relationship of mutual acceptance and confidence of positive value in conditioning the infant to later changes in methods of feeding and subsequent training.

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INCIDENCE OF TUBERCULOSIS AMONG 2,562 HIGH SCHOOL STUDENTS IN A SUBURBAN CITY

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EAST ORANGE, N. J.

THE legislature of the state of New Jersey in August, 1939, passed certain laws relating to the health of the school pupils and school employees. Among these was one which stated that the "board of education of every school district shall periodically determine or cause to be determined the presence or absence of active tuberculosis in any or all pupils in public schools" in accordance with regulations later to be established by the State Board of Education. Subsequently the State Board of Education ruled that a tuberculin test should be given annually to all pupils of the ninth, tenth, eleventh, and twelfth grades, i.e., to the high school group, and that positive reactors should have an x-ray examination of the chest. Thus for the first time a tuberculosis survey of certain important large groups of our school population became mandatory, making it an important milestone in the progress toward eventual eradication of this serious disease. The content of this paper deals with the methods used in carrying out the tests in a group of 2,562 high school pupils in a large suburban city (population, 70,000) and with an analysis of the results obtained.

After the forearm had been washed with acetone, there was applied a tuberculin patch test (Vollmer). No bathing of that forearm was allowed until the patch test was removed by the school doctors two days later, and final readings were made two days after the removal of the patches. The tests were read in the usual manner, although if any red papules appeared after the final readings, those tests were also considered positive. All the positive reactors were required to have an x-ray examination of the chest, which was done on paper films 14 by 17 inches in size. These films were interpreted by a team of three men, two of them roentgenologists at our local hospitals and the third a clinician of wide experience, specializing in tuberculosis. In the few cases where the paper films were not satisfactory, repeat stereoscopic plates on celluloid films were taken.

Testing was done in the two senior high schools and one junior high school of the city. The junior high school is located in a section where many Italian and negro families are represented; High School X is in a residential district of the better type, and High School Y includes a more cosmopolitan group of pupils.

The incidence of positive reactors found in this group of high school pupils taken as a whole was 15 per cent. This result compares very

favorably with that found in three adjoining communities where the incidence of positive reactors varied from 18 to 31 per cent (12,971 tested) and with that of the entire county where the percentage was 23.7 (1939 figures). The incidence of positive reactors did not vary greatly among the three schools (Table I). In the junior high school located in the center of the lower economic section of the city, the percentage was 14.5, while in High School X, situated in the better section, the percentage was 12.2, and in High School Y with a mixed group it was 17. While these figures do not differ sufficiently to be very significant, they do bear out the common belief that tuberculosis is less frequently found in the economically better situated groups of society.

When the positive reactors are divided according to their grade in school, the figures do not vary much, being 14.9 per cent for freshmen, 14.5 per cent for sophomores, 16.4 per cent for juniors, and 16.1 per cent for seniors. Although a slight trend toward a greater incidence of positive reactors is indicated in the higher grades, the difference is not particularly significant.

A study of these same students divided according to their race shows to a large extent the same uniformity of positive reaction existing among the whole group (Table II). The white American and Italian groups show a rate of 15 per cent, exactly the same as the general incidence, while the miscellaneous group (Greek, Chinese, South American, etc.) gives an incidence only slightly higher, 17.7 per cent, although the number of students in this group, twenty-four, is very small. Of 216 Negro students, forty-seven, or 21.1 per cent, were positive reactors, 6 per cent above the general average, while three, or 6.4 per cent, of the forty-four Jewish pupils were positive reactors, far below the average incidence. The 6 per cent showing of the Negroes above the average incidence, while small, is in keeping with the usual findings in this race, and suggests that, at least in this community and for this disease, conditions are pretty uniform throughout the city.

Table III shows the different incidence of positive reactors in the male and female students, the rate being 53 per cent for the males and 47 per cent for the females. A quick glance at the table, however, shows clearly that this situation was exactly reversed in some of the grades, indicating what erroneous deductions could be made from small numbers of cases.

In the interpretation of the x-ray films, the classification and diagnostic terms established by the National Tuberculosis Association and commonly accepted throughout the state were used: Class A, primary tuberculous infection without demonstrable lesion (positive test and negative x-ray); Class B, primary tuberculous infection with demonstrable lesion (positive patch test and primary complex on x-ray); and Class C, reinfection type tuberculous infection (adult type) which is subdivided into group 1, active, and group 2, inactive. Films falling into Class A can therefore be considered negative, and those falling into

TABLE I

INCIDENCE OF POSITIVE REACTORS TO TUBERCULIN PATCH TESTS BY SCHOOLS AND GRADES

GRADE	JR. HIGH SCHOOL				HIGH SCHOOL X				HIGH SCHOOL Y				TOTAL				GRAND TOTAL
	+	%	-	%	+	%	-	%	+	%	-	%	+	%	-	%	
9	26	14.5	153	85.5	22	12.1	159	87.9	59	13.8	296	86.2	107	14.9	608	85.1	715
10					24	12.2	172	87.8	71	15.4	389	84.6	95	14.5	561	85.5	656
11					27	14.3	161	85.7	71	17.4	336	82.8	98	16.4	497	83.6	595
12					18	10.0	161	90.0	78	17.9	339	82.1	96	16.1	500	83.9	596
Total	26	14.5	153	85.5	91	12.2	653	87.8	279	17.6	1,360	83.0	396	15.0	2,166	85.0	2,562

TABLE II

INCIDENCE OF POSITIVE REACTORS ACCORDING TO RACE AND SCHOOL

	AMERICAN				JEWISH		ITALIAN		MISC.		TOTAL	
	WHITE		NEGRO									
	POS.	NEG.	POS.	NEG.	POS.	NEG.	POS.	NEG.	POS.	NEG.	POS.	NEG.
JUNIOR HIGH SCHOOL												
Boys	3	37	0	11	0	6	5	23	1	0	9	77
Girls	9	31	4	13	0	0	4	32	0	0	17	76
Total	12	68	4	24	0	6	9	55	1	0	26	153
HIGH SCHOOL X												
Boys	40	282	0	12	0	3	5	14	2	2	47	313
Girls	39	311	3	7	0	5	2	14	0	3	44	340
Total	79	593	3	19	0	8	7	28	2	5	91	653
HIGH SCHOOL Y												
Boys	119	510	16	55	2	17	16	74	1	7	154	663
Girls	93	540	24	71	1	13	6	61	1	12	125	697
Total	212	1,050	40	126	3	30	22	135	2	19	279	1,360
Grand total	303	1,711	47	169	3	44	38	218	5	24	396	2,166
Per cent	15	85	21.1	78.9	6.4	93.6	15	85	17.7	82.3	15	85

TABLE III

INCIDENCE OF POSITIVE REACTORS ACCORDING TO SEX

GRADE	BOYS	GIRLS
JR. HIGH SCHOOL		
9	9	17
HIGH SCHOOL X		
9	12	10
10	10	14
11	13	14
12	12	6
HIGH SCHOOL Y		
9	28	31
10	44	27
11	43	28
12	39	39
Total	210	186
Per cent	53	47

TABLE IV

SHOWING RESULTS OF X-RAY EXAMINATIONS OF CHESTS OF POSITIVE REACTORS

GRADE	A	B	C	% B & C	C-1	C-2	TOTAL
9	83	23	1	22.4	0	1	107
10	81	13	1	14.7	1	0	95
11	81	16	1	17.3	0	1	98
12	79	14	3	17.7	1	2	96
Total	324	66	6	18.1	2	4	396

Classes B and C, positive, although in a sense Class B films can be considered negative, since the shadows they reveal represent healed and quiescent lesions.

Of the 396 x-ray examinations made of the chest, 324 (81.9 per cent) fell into Class A—entirely negative films; 66 (16.6 per cent), fell into Class B—negative so far as present activity was concerned but positive in the sense that previous tuberculous infections were evident on the films; and only 6 (1.5 per cent) fell into Class C—reinfection type cases. Of these six, one was definitely active, one possibly so, and four apparently inactive. Classes B and C together represent 18.1 per cent of those x-rayed and only 2.7 per cent of the entire student body. The finding of only two active cases, seven hundredths of 1 per cent among 2,562 students, is considered an excellent health record for a community of this size and character.

An interesting sidelight in this study was the frequency with which close questioning in these reinfection cases revealed contact with a definite or a probable active case of tuberculosis. Four out of six gave a positive history. A few examples are as follows: The mother of one of the C-1 students, we learned, had died of meningitis in March, 1941. Inquiry at the hospital revealed that the clinical diagnosis had been tuberculous meningitis. The father of one of the students with an inactive case had died of pulmonary tuberculosis two years previously. He is stated to have had his original infection in 1926. The process became arrested and then he relapsed in 1939. The aunt of a third student had gone away to the Adirondacks eight years before for her health. The aunt had been living in the student's home prior to going away to the mountains. When the patch tests, combined with the x-rays of the positive reactors, point to certain suspicious cases, and then further questioning confirms definite family contacts, it leaves one with a conviction that here we have a relatively simple but highly accurate method of picking out the active and potentially active cases from a large group of individuals.

TABLE V

ITEMIZED EXPENSES OF TUBERCULIN TESTING PROGRAM

Patch tests	$107.00
Cotton and acetone	10.72
Tuberculosis league for descriptive pamphlets	15.00
X-rays	350.25
Doctors' services	151.90
Total	$634.87

Itemized in Table V are the expenses connected with carrying out this tuberculin testing campaign. In view of the number of students tested (2,562) and x-rayed (396) and the number of actual (2) and potential (4) cases found, the total cost of $634.87, or 25 cents per pupil, seems very small. The average cost of treating a patient at the sana-

torium has been computed to be $1,084 per year. Since only one of the six students with reinfection type cases required institutional care, an expenditure of $634.87 has saved the taxpayers of the community the cost of supporting five persons at the sanatorium for an average of eighteen months each, approximately $8,000. More important, however, is the saving in human lives, for now that the existence of their infection is known, progression of their lesions should not occur. If these cases had gone unrecognized, all might have become well advanced before coming under proper treatment, with the resultant loss of health, money, and job.

SUMMARY

The results of a tuberculosis testing campaign among the high school students of East Orange, N. J., are reported. Two thousand five hundred and sixty-two students were tested with the patch test, of whom 15 per cent reacted positively. The lowest percentage was in the tenth grade, 14.5 per cent; the highest was in the eleventh grade, 16.4 per cent. The 216 negro students gave a rate of 21.1 per cent. Boys gave a higher incidence than girls; 53 per cent compared with 47 per cent.

Of the 396 students whose reactions were positive and who were x-rayed, 72, or 18.1 per cent, showed evidence of the primary complex or reinfection type of the disease. There were six of the latter, two active and four inactive. All were white American children. Two active cases represent 0.07 per cent of the high school student body.

The cost of testing and doing the necessary x-rays of 2,562 students was $634.87, or 25 cents per student.

610 PARK AVENUE

Critical Review

RECENT ADVANCES IN THE STUDY OF POLIOMYELITIS

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FEW diseases have yielded more slowly to scientific analysis than has poliomyelitis. After more than a quarter of a century of research we still lack the fundamental knowledge necessary to suggest a practical measure for its control. Nevertheless, our knowledge of this disease is advancing, though not without the necessity of some revisions of what were once regarded as settled facts. I have been asked to present some of the more recent advances and to interpret them so far as I am able.

PROPERTIES OF THE VIRUS

The agent of poliomyelitis is a filtrable virus which shares with other members of the virus group such general properties as intracellular relationship, dependence on living cells for growth, cell specificity, etc. The particle size of one extensively studied strain (MV) is known to be approximately 10 mμ, or about twenty times smaller than can be seen with a good microscope. Whether all strains fall into this order of magnitude is yet to be determined.

The virus is remarkably resistant to physical and chemical agents. It withstands drying in vacuo for at least a month and exposure to 50 per cent glycerine for several years. It is resistant to many chemical agents in concentrations likely to exercise either an antiseptic or a germicidal action on bacterial forms of life. We recently tested the resistance of one strain (MV) against more than a hundred chemical agents. Less than ten inactivated the virus in vitro when employed in concentrations of 0.1 per cent. Among these were copper sulfate, mercurochrome, mercury bichloride, oxyquinoline sulfate, potassium hydroxide, and potassium permanganate. Kempf and Soule[1] have recently reported that chlorine in a concentration of 0.5 p.p.m., an amount in excess of that usually employed in water purification, failed to inactivate the virus within one and one-half hours. It is quite resistant to such protoplasmic poisons as ether, basic lead acetate, and phenol (1 per cent), to gastric and intestinal juices, and to bile.[2] The extent to which individual strains may differ from each other in their resistance to physical and chemical agents is still unknown.

During the early part of the past decade several attempts were made to purify and concentrate the virus by chemical and physicochemical means. These were attended with some degree of success but also with considerable loss of virus. In 1937, Schultz and Raffel[3] showed that the virus can be sedimented from almost water-clear aqueous suspen-

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sions by means of the air-driven vacuum ultracentrifuge, operating for several hours at speeds of about 30,000 r.p.m. This was confirmed by Clark,[4] who has combined chemical procedures and differential centrifugation in an effort both to purify and concentrate the virus. Loring,[5] at Stanford, is now using differential centrifugation in an attempt to obtain the virus in a pure state for the purpose of chemical analysis. Thus far he has succeeded in obtaining concentrations of the virus 10,000 to 100,000 times that represented in the spinal cord of a paralyzed monkey. A seemingly pure product has proved infectious for monkeys by the intracranial route in a dilution of 1 in 200 million. Chemically the virus seems to consist entirely of protein, or of protein in combination with nucleic acid.

Although many viruses have been cultivated in the presence of growing embryonic cells, often derived from animals quite unrelated to the natural virus hosts, efforts in this direction with poliomyelitis virus have in the past proved relatively unfruitful. The only investigators to report conclusive results were Sabin and Olitsky[6] in 1936. Their results were realized with a medium which contained fresh nervous tissue from *human* embryos, obtained by cesarean section. Nervous tissue from the monkey, mouse, and chick, as well as the nonnervous tissues from the same human embryos, failed to provide the pabulum necessary for growth. Their observations indicated clearly that this strain (MV) had retained a high degree of specificity for human nervous tissue in spite of the fact that it had been passed in monkeys for more than twenty years.

This was the situation until recently. Within the past year, Jungeblut and Sanders[7] have announced the cultivation of another strain, the SK strain, in this instance, however, in the presence of embryonic *mouse* brains. This strain originally was isolated from the stools of a case of abortive poliomyelitis by Trask, Vignec, and Paul,[8] and previous to its cultivation was adapted by Jungeblut and Sanders to white mice. On intracerebral inoculation into mice, a culture of the fourteenth generation produced infection in dilutions as high as 1 part in a billion, a titer which, incidentally, is considerably in excess of the titers reached by previously known strains based on inoculations into monkeys (rarely as high as 1:10,000). The pathogenicity of the cultured virus for monkeys was limited. I shall refer to this strain again later.

EXPERIMENTAL HOST SUSCEPTIBILITY

Until two years ago, all efforts to transmit the disease to animals other than monkeys and chimpanzees were unsuccessful. Not only all common laboratory animals but all new world species of monkeys tested had proved resistant. This restriction to costly animals has had a decided limiting effect on the scope of research on this disease. However, late in 1939, Armstrong[9] both surprised and delighted workers in the field with the announcement that he had succeeded in adapting a recently isolated strain to a newly tested rodent, the southern cotton rat (Sigmoden hispidus hispidus). The virus strain used came from a fatal case of bulbar paralysis in Lansing, Mich., and is now widely known as the "Lansing strain." Prior to his initial report he had succeeded in carrying this strain through seven passages in cotton rats. Rat brains from second and fifth passage induced typical poliomyelitis in monkeys. In a later report[10] he created further surprise by announcing that he had succeeded in adapting this strain from the cotton

rat to the white mouse. Following this, Jungeblut and Sanders[7] reported the adaptation of the SK strain, referred to under cultivation of the virus. This strain was also carried first to cotton rats and then to white mice. It differed from the Lansing strain in that the adaptation was attended with a marked drop in pathogenicity for the monkey. Lately, Jungeblut and Sanders[11] have reported a further adaptation of the SK strain from the mouse to the guinea pig. In the guinea pig, however, serial passage was associated with a lengthening of the incubation period, from two to four days in the beginning to seven to twenty-one days later on. Two attempts at serial passage came to an abrupt end with the fifth and sixth passages, respectively, but a third line was carried through ten generations. During the period that the virus was still active in guinea pigs, it could be returned easily to mice and cotton rats but not to the rhesus monkey. However, "when its virulence diminished for guinea pigs and mice, intracerebral inoculation of a rhesus monkey with material from the cord of a paralyzed guinea pig resulted, eight days later, in classical poliomyelitis." They suggest that some cyclic change in the pathogenicity of the virus may have been responsible for this result.

Toomey and Takacs[12] have recently reported observations on two old well-identified strains (MV and Philadelphia) previously regarded as infectious only for monkeys. When these two strains, along with seven others, were first inoculated intracranially into cotton rats, they failed to induce the paralytic disease. However, when cotton rats inoculated intracranially with either of these two strains were injected simultaneously by the subcutaneous route with a toxic filtrate of mixed cultures of certain enteric bacteria ("enteric organism filtrate"), a paralytic infection was induced which could then be transmitted serially without the enteric filtrate. One of the two strains (MV) so adapted was successfully returned to the monkey after eleven passages in cotton rats; the other strain apparently was not so tested.

While the results of these adaptation studies leave one with a sense of *fait accompli*, it may be well to await the results of further investigation, designed to establish more clearly the identity of the strains presumably adapted to the respective rodents. Unfortunately, such adaptation studies are complicated by the fact that certain rodents are now known to be victims of paralytic diseases under natural conditions. A naturally occurring flaccid paralysis in guinea pigs was described thirty years ago by Römer.[13] It was associated with lesions similar to those present in human poliomyelitis and was caused by a filter-passing virus. Similar, though less complete, observations were later reported by Neustaedter[14] and by Picard.[15] Although in all three instances the guinea pigs had been in close association with poliomyelitic monkeys, it was not determined whether they owed their affliction to the same virus.

Seven years ago Theiler[16] reported a spontaneous and sporadic flaccid paralysis among his stock mice. It was associated with a poliomyelitic type of lesion in the cord and was shown to be caused by a filter-passing virus. Recently, Theiler,[17] and Olitsky,[18] have reported detailed studies on this disease and revealed a number of respects in which the disease parallels that of human poliomyelitis, even to the size and general properties of the causal agent. However, none of the several strains tested thus far have proved infectious for monkeys. This would seem to provide a dependable means for distinguishing human and mouse strains, though more observations are probably nec-

essary to make certain that this is the case. Offhand it would seem no less possible for rodent strains to prove transmissible to monkeys than for certain human strains to prove transmissible to rodents.

It is possible to clear up to some extent uncertainties arising from the existence of such natural diseases in experimental animals. By means of the neutralization test, using a specific homologous antiserum, it should be possible to identify a virus as still the same after its supposed adaptation to another species of animal, assuming, of course, that the antigenic properties of the virus have not been greatly changed by serial passage in the new host. By cross immunity tests, its identity may be further proved.

The initial identification of a new strain may have to depend at times on the clinical and pathologic picture produced in monkeys. In other words, serologic and immunologic proof that the strain has actually been derived from the patient and is a true human strain may not always be obtainable. Studies on the antigenic properties during the past decade have revealed that strains may not only exhibit quantitative differences, serologically and immunologically, but outright qualitative differences. The latter type of difference was first recognized by Burnet and MacNamara[19] about ten years ago. They observed that monkeys which had recovered from a newly isolated Australian strain were still susceptible to an American strain (MV) and, further, that serums from respective convalescent animals served to neutralize only the homologous strain. Similar qualitative differences have been reported since by several other investigators,[20] while quantitative differences are probably not uncommon.

In the present connection we are concerned primarily with the serologic and immunologic identity of strains presumably adapted from monkeys to rodents. If the original properties of a strain are known and the technical procedures are sufficiently rigid to exclude sources of error, it should then be possible to keep fully informed on its continued identity during the course of its adaptation to another species of animal. With regard to the adaptation of the Lansing strain to cotton rats and mice. Armstrong[10] in his second paper has submitted some serologic evidence indicating that the adapted virus is still a strain of human poliomyelitis virus. In a subsequent report in collaboration with Haas,[21] he presents additional evidence based on human sera from two regions in which poliomyelitis has recently occurred, Detroit, Mich., and Charleston, S. C. Of a total of eighty-three sera tested from these regions, 68.7 per cent neutralized the mouse passage virus.

Jungeblut and Sanders[11] also have submitted serologic evidence to show that their mouse adapted SK strain is still related to the monkey passage virus and to two other known strains. Their tests were carried out with undiluted sera in a ratio of 10 parts of serum to 1 of varying dilutions of virus, a ratio which, to my mind, does not yield as convincing results as one in which the serum is diluted and the amount of virus is kept constant. A more complete comparison of the antigenic properties of the mouse passage virus with the monkey passage virus would have proved helpful and of interest in the case of both the SK and the Lansing strains, one in which the dilutions of serum were varied in one series of tests and the amount of virus in the other.

In a paper which followed their initial report on the adaptation of two older laboratory strains, Toomey and Takacs[12] have submitted

reasonably satisfying serologic evidence in support of the identity of one of the strains (MV) adapted to the cotton rat. In a paper just off the press, similar supporting evidence has been submitted for the second strain (Philadelphia).[22] In this serologic study they included also the cotton rat adapted Lansing strain and the cotton rat-mouse adapted SK strain, which had been supplied to them by Jungeblut and Sanders. It was observed that while the Lansing strain was neutralized by the convalescent serums used, the murine SK was unaffected. This then raises a question regarding the identity of the murine SK virus and further emphasizes the need for a more complete serologic comparison of adapted strains with parent and related strains.

PORTAL OF ENTRANCE

We turn now to a consideration of the portal by which the virus gains entrance to the body. Until recently, it was widely held that the common natural portal of entry for the virus of this disease is the olfactory portion of the nasal mucosa.[23] It was believed to spread from this area in the nose along the olfactory nerve to the olfactory bulbs and from there along the olfactory tracts to the central nervous system. A small minority held that invasion might occur through other mucous surfaces, more particularly through the mucosa of the digestive tract. In addition to finding the virus in the stools of patients on individual occasions, it had been possible at times to induce infection in monkeys merely by feeding the virus, or by introducing it by stomach tube. The occasional presence of virus in the stools of patients was accounted for by the majority group on the assumption that it had been swallowed with nasal and mouth secretions. Moreover, the results of earlier feeding experiments had proved difficult to confirm.[24] At the same time, the evidence on which the majority belief rested was not of a substantial character in so far as this related to the human disease. In monkeys it had been well established that infection could easily be induced merely by instilling virus intranasally. Extensive studies carried out with a certain widely used experimental strain (MV) had established beyond any doubt that when infection was so induced, invasion of the central nervous system occurred solely along the olfactory pathway and not along other possible pathways. This was evident from inflammatory infiltration along the olfactory pathway, from the presence of virus in the olfactory bulbs, from the fact that surgical interruption of the olfactory tracts definitely prevented infection by the intranasal route, and finally from the fact that chemically induced changes in the olfactory mucosa serve to prevent infection.[23] These observations indicated a high degree of neurotropism on the part of the virus and a remarkable dependence on the olfactory mechanism for its migration from the nasal mucosa to the central nervous system. This close association of the portal of entry with the olfactory mechanism was clearly understandable from the general structure of the olfactory mucosa, through which the initial step of the invasion obviously occurred. In this area and in that occupied by the organ of taste in the tongue ("taste buds"), we have the only regions where nerve endings are nakedly exposed to the exterior. Assuming that there is a highly neurotropic virus on the mucous surfaces, these are then the only regions where the virus can realize immediate contact with nerve cells. The prominence of this anatomic feature with relation to the olfactory mechanism and the highly selective properties of the virus made it understandable why any break in

this nervous pathway, either peripheral or central, sufficed to prevent infection. And, the great regularity with which such breaks served to prevent infection afforded a strong argument against the probability that the virus possessed any significant power to penetrate mucous membranes not associated with such exposed nerve endings.

These were the observed facts in monkeys. In man, however, the olfactory pathway as a natural and common portal was not so well established. Though virus had been recovered from nasopharyngeal washings of a limited number of cases, convalescents, and contacts,[25] it is a surprising fact that more direct observations on the olfactory pathway in man were seldom made. Olfactory bulbs from fatal human cases were rarely included in routine post-mortem examinations. Only recently has attention been more systematically directed to these structures. The results of these belated observations now fail to lend support to the generally held view, that in man also the olfactory pathway affords the most natural route. The first to question this was Smith[26] in 1934. Of fifty-six olfactory bulbs examined (from about forty cases), less than a fourth showed inflammatory infiltrations indicative of the virus having passed through them. The following year Horányi-Hechst[27] reported that he had found no changes whatever in fifteen bulbs examined. Similar negative observations have since been reported on cases from Arkansas by De Groat,[28] from Australia by Swan[29] and Robertson,[30] and very recently from the eastern part of the United States by Sabin.[31] Although less than 100 cases have been covered and these may not reflect the situation in all epidemics, the observations reported are by no means in harmony with those which have been made on monkeys, in which a trail of inflammatory reaction apparently always marks invasion by the olfactory pathway. Such negative observations in man must mean either that the virus does not frequently enter by this pathway or that it commonly does so without leaving a trail of inflammatory reaction. The latter possibility cannot be wholly disregarded, for although it is true that infection by the intranasal route in monkeys is usually associated with extensive round cell infiltration in the olfactory bulbs,[32] we have observed that under certain experimental conditions this may be very slight indeed. It is possible, therefore, that in man, who, by virtue of his natural susceptibility, may be infected by much smaller amounts of virus than is commonly employed to induce infection in monkeys, little or no reaction may be elicited by this initial step in the invasion.

I have seen olfactory bulbs from only two human cases. Both showed extensive infiltration. Such isolated instances, however, cannot be said to provide conclusive evidence that the virus even at times enters by the olfactory pathway, since it is also possible for such infiltrations to arise from a centrifugal spread of the virus; that is, from the central nervous system to the bulbs. Although it has been reported that in monkeys infiltration of the bulbs is evident only following intranasal inoculations,[22, 33] I have, on a number of occasions, observed marked infiltration in the bulbs and olfactory nerve filia in animals infected by the intracerebral route. A similar centrifugal spread might therefore occur at times also in man.

But the absence of inflammatory infiltrations in the bulbs does not constitute the sole evidence against the olfactory pathway. There have also been failures to demonstrate the presence of virus in human olfactory bulbs.[34] Although such examinations have been few in number and a negative result does not always exclude the possible presence of virus,

these negative findings do carry weight when added to the negative histologic observations just mentioned.

In connection with these negative findings, it seems important to bear in mind that the present status of our knowledge of the role of the olfactory pathway still rests on limited observations which may not necessarily reflect the relationship in all epidemics and that pathologists should in the future systematically include olfactory bulbs in their autopsy examination and report their observations, or forward the bulbs to investigators for examination.

Offsetting the negative results with relation to the olfactory pathway, there is a rapidly growing body of evidence indicating that the common portal may be the pharyngeal mucosa, the mucosa of the intestinal tract, or both. This evidence rests in part on a demonstration of virus within these tissues and especially in stools. Particularly do they rest upon infections induced in experimental animals, either by feeding the virus or by applying it directly to mucous surfaces.

Knowledge that the virus may be found in stools is not exactly new. This was first demonstrated by Kling, Pettersson, and Wernstedt[35] more than twenty-five years ago. Scattered instances were subsequently reported, but only since 1937 has there been a growing realization of the frequency and ease with which the virus can be demonstrated in the stools not only of paralytic patients, but also of abortive cases, convalescents, and contacts. In 1937, Harmon[36] demonstrated it in the rectal washings of four patients. Similar observations have been reported since by a number of investigators in this country and abroad. In this country, Paul and Trask[37] have been especially active in these studies. One of their more outstanding contributions has been the demonstration of virus in sewage. Identification of the virus in stools, sewage, and other contaminated materials has been facilitated by the discovery that such material need merely be instilled intranasally into monkeys,[38] though it is believed that the simultaneous intraperitoneal injection of the animal with ether-treated material serves to increase the chance of demonstrating the presence of the virus.[39] Tests such as these have revealed that the virus is not only frequently present in stools, but that it may be present in relatively large amounts and demonstrable there with greater ease and regularity than in nasopharyngeal washings.

An interesting parallel has been found in Theiler's encephalomyelitis of mice ("mouse poliomyelitis"), referred to earlier. Olitsky[18] was able to recover the virus of this disease from the intestinal contents of practically all of his adult stock of white mice, while Theiler and Gard[17] found it in approximately two-thirds of 6-month-old mice. Olitsky and Schlesinger[40] have just reported its presence in the intestines of normal wild gray house mice. The carrier state in white mice is apparently acquired soon after weaning. Although a high per cent of adult mice show it, only 1 mouse in about 3,000 to 5,000 develops paralysis. The almost regular presence of virus in the intestinal contents raises the fundamental question as to its genesis. This is of interest because of our knowledge of the growth requirements of viruses in general and of neurotropic viruses in particular. That it multiplies in the intestinal contents seems quite unlikely. Where then does it multiply—in the intestinal or the nasopharyngeal mucosa or within some deeper tissues, whence it may be excreted in some way into the lumen of the gut? We should also like to know whether in man

the carrier state for the human poliomyelitis virus is as general and prolonged as that found in the case of Theiler's virus in mice.

The most convincing evidence that the digestive tract may be an important portal of entry has been obtained from recent infection experiments, especially those in which measures have been taken to exclude the possibility of infection by the olfactory pathway. No doubt the question which immediately arises in your minds is this: Why was this not settled earlier? Certainly it was not because it had been allowed to go untested. Indeed, several earlier investigators had obtained results suggesting that infection may occur from the digestive tract, but their results, which were by no means uniform, had proved difficult to confirm.[24] An important reason for this difficulty will be presented a little later.

Since in ordinary virus feeding experiments there is always the possibility of infection by the olfactory pathway as the result of chance contamination of the nasal mucosa, I shall omit reference to all earlier experiments in which no attempts were made to exclude infection by that route. This includes experiments in which the virus was given by stomach tube, for even with this method there can be no assurance against subsequent contamination of the olfactory mucosa by regurgitation or vomiting. However, experimental results based on exclusion of the olfactory pathway are now available. The first work of this kind was reported about two years ago by Burnet, Jackson, and Robertson[41] of Australia. These investigators successfully induced the disease in *Macacus cynomolgus* monkeys by merely swabbing a recently isolated strain (Mar.) over the pharyngeal and tonsillar mucosa, or over the tongue. Some of the monkeys in which the infection was induced had been previously given an intranasal instillation of a 1 per cent solution of zinc sulfate to rule out infection by the olfactory route.* Though the cynomolgus monkey was found more highly susceptible to the virus than the rhesus, they attribute their success much more to the properties of the virus strain used than to the species of monkeys. This is borne out by the negative results which Flexner[24] had obtained several years earlier with the same species of monkey but using another strain of virus (MV). That not all newly isolated strains of virus readily induce infection in this way is reflected by the negative results of three successive feeding experiments which I have carried out on six cynomolgus monkeys with a strain recently recovered from the stools of a patient.

Howe and Bodian[42] in a similar experiment employed chimpanzees as test animals and a pool of virus positive stools from human cases as the virus inoculum. The purpose in using the latter was to eliminate any possible modifying effect which passage in monkeys might have on the native properties of the virus. The employment of the chimpanzee was suggested because of its close phylogenic relationship to man, and also because of a recent report indicating that during an outbreak in Cologne, Germany, two chimpanzees in a children's zoo

*Unfortunately, the authors do not state when, with relation to the zinc sulfate treatment, the virus was applied. However, one receives the impression that the zinc sulfate treatment immediately preceded the application of virus. If this is true, there is then a possibility that the olfactory pathway was not definitely excluded. We have found that the protection conveyed by zinc sulfate does not become fully effective until after a lapse of two or three days, and that more than half of the animals may develop infection if inoculated within twenty-four hours after the chemical solution is applied. The uncertainty which this raises, unhappily, is not settled by the incorporation, in their report, of any confirmatory histologic observations on the olfactory bulbs. Except for examining "a portion of the olfactory bulbs" from one animal *for virus*, no evidence was submitted which would definitely exclude infection by the olfactory pathway.

had contracted the disease by natural contagion. One of these animals died and showed cord lesions characteristic of poliomyelitis. Howe and Bodian gave three of the chimpanzees large amounts of stools by stomach tube. The olfactory tracts of one of these had been cut four or five days previously to exclude infection by the olfactory pathway.* A fourth animal, in which the olfactory tracts also were cut, was given a suspension of the stool by mouth while the animal was under light anesthesia. A fifth animal, without severed olfactory tracts, was instilled intranasally with the virus stool suspension. All of the animals, excepting one of the three given stools by stomach tube, developed the disease. Of these only the animal which was instilled intranasally showed definite lesions in the olfactory bulbs. In two of the animals, including one in which the tracts had been cut, a meningitis was observed around the "olfactory nerve filia" in one case and around the olfactory bulbs in the other, which they regarded as merely an extension of a generalized meningitis observed over all the exposed pial surfaces of the brain.† Although the spinal cords of all four chimpanzees showed extensive lesions typical of the disease, when suspensions of three of these were inoculated intracranially into rhesus monkeys, one failed to induce infection. This observation confirms earlier experiences with human material, in that it is not always possible to demonstrate the presence of virus even though lesions are evident. Either the sudden transfer to a new host or a rapid autosterilization may account for it.

Recently Trask and Paul[43] have reported two feeding experiments in which they used the green African monkey and the SK strain referred to earlier. Of eight green monkeys included in two distinct feeding tests, one developed paralysis with cord lesions but showed no lesions in the olfactory bulbs. A questionable paralysis with doubtful lesions in the cord was observed in a second and merely a febrile temperature rise in a third.

The foregoing represented observations on experimental animals. At a meeting last December, Sabin and Ward[34] presented observations on the distribution of virus in human autopsy material, which bear directly on this question of the portal of entry in man. The results of a detailed study on seven cases are of considerable interest. Of foremost interest is the fact that in none of the cases was virus demonstrable in the olfactory bulbs. The nasal mucosa also was negative in all cases, but virus was present in the pharyngeal mucosa alone or in pharyngeal mucosa together with the tonsils in three and possibly four of the cases. It was present in the central nervous system in all of the patients and its presence here was more easily demonstrated in those who died soon after the onset of illness than in those who died later. It was found in the wall of the ileum in three patients and in the contents of the ileum in two. It was present in the contents of the descending colon in six (one was not examined) and in the washed wall of the colon in one of the six. Surprisingly enough it could not be demonstrated in the mesenteric lymph nodes and in only one patient in the abdominal sympathetic nerve ganglia (celiac). This left a substantial

*We believe that in experiments of this type it would be safer to allow several weeks for healing of the operative wound to take place before putting animals into the final part of the experiment.

†I should like to say parenthetically that such interpretations must be made guardedly since infiltrations following *intranasal* infection in monkeys may at times be limited to the meninges and outer zone of the bulbs.

gap between the two systems in which virus was most easily demonstrated; namely, the alimentary tract and the central nervous system.

A part of their study dealt with the secretion or excretion of virus in patients suffering with the paralytic disease. In this part of the study they examined nasal and oral secretions as well as stool or enema returns for the presence of virus. Although it was demonstrable in the stools in nine of twenty-three cases, it was not detected in any of the cases in the nasal secretions or saliva.

From these various observations, it is apparent that the hitherto held view that the olfactory pathway affords the common portal is not supported by the results of recent investigations and that the evidence at present points more to other mucous membranes, pharyngeal or alimentary, as the common portal.

Burnet[44] in a recent article based on an analysis of epidemiologic literature and on observations drawn from the 1937-1938 epidemic in Victoria, Australia, postulates that an important change in the disease has occurred during the past thirty or forty years. He believes that the virus has shifted from an essentially epitheliotropic virus, commonly producing a recurrent nonsymptomatic infection in adults, to one which is now more neurotropic and which is spread chiefly by contact of older children with each other. His thesis rests in part on a difference in age distribution prior to 1920 and now. The disease in earlier times was primarily one of very young children, while at present the average age corresponds more closely to that of other common infections of childhood. He suggests that prior to 1887 the virus was one of low virulence but high infectivity, causing widespread mild recurrent infections, probably mainly of the pharyngeal mucosa, with the production of some antibody and immunity. At that time it revealed itself only rarely by inducing paralysis and then almost exclusively in infants or very young children as the result of infection transmitted from intimate adult associates. In recent years the virus has shown itself to be more neurotropic, less infective, and less antigenic or immunizing. With the development of this difference there has been a tendency for the widespread reservoir of adult infection to disappear, and consequently the risk to infants. The disease according to Burnet is now spread chiefly by contact of children with each other and during the age period when contact between children is close and intimate.

You may have noted that Burnet emphasizes the pharyngeal mucosa as the natural locus of this virus. The recent observations by Sabin and Ward[34] on the presence of virus in the pharyngeal mucosa in human autopsy material is in harmony with this view and suggests that in the future attention should be directed to the possibility that this may be the common portal.

This then is the present status of our knowledge bearing on the portal of entry. We may now review briefly what is known regarding the relationships of the virus after it has passed the epithelial barrier.

PATHOGENESIS AND PATHOLOGY

Observations on both human and monkey material have revealed that once the virus has become established in the nervous system it remains very intimately associated with this system throughout the course of the disease. Although the nature of its initial relationship within such epithelial structures as the pharyngeal or intestinal mucosa is still unknown, its affinity for extranervous tissue appears to be of a low order. It

apparently never appears in the blood in detectable amounts and is rarely demonstrable even in the spinal fluid. It is seldom present in lymph nodes, except when nodes receive the drainage from a virus-contaminated focus. Within the nervous system it is associated with the neurones rather than with the supporting tissues. A close association with neurones is evidenced by its spread within the nervous system along axonal pathways and also by the fact that the earliest and most prominent pathologic change may be death of nerve cell bodies. Although the primary neuronal character of the disease was suggested by certain early reports on human material, experimental evidence of a very close association of the virus with neurones was not provided until 1930. At this time Fairbrother and Hurst[45] reported observations on monkeys made during the preparalytic stage of the disease, which showed quite conclusively that the virus spreads along nerve processes, apparently as an intraneural infection. Their observations have been confirmed and extended by others.[46] We need not be concerned here with the question of precisely which are the preferred neuronal pathways but merely with the more fundamental fact of its axonal spread. Whatever the peripheral point of invasion, whether olfactory or from some other point, the virus apparently always spreads along the peripheral nerve to the central nervous system, within which it then spreads to different levels along certain preferred neuronal pathways. From the central nervous systems, it may in turn spread centrifugally into previously uninfected peripheral nerves.

A wide dissemination of the virus in the nervous system may not appear in harmony with the limited involvement which frequently marks the disease. To understand this seeming contradiction it is necessary to put aside the assumption that nerve cell damage is always a consequence of exposure to virus or that virus has reached only those parts of the central nervous system suggested by the distribution of the paralysis. Two years ago, we reported[47] observations which not only supported the theory of neuronal (axonal) spread within the central nervous system, but also revealed that during the early preparalytic period of the experimental disease high concentrations of virus may be found in certain regions of the brain, through which it passed en route to the medulla and cord, though the nerve cells in these regions rarely present evidence of damage. It was also observed that quite high concentrations of virus were present in the cord before the onset of any paralysis, the latter apparently being suddenly precipitated after the concentration had shifted to a little higher level. Our observations seemed to warrant the conclusion that the fate of the nerve cells concerned in the propagation of the virus depends on two general factors: (1) on the general level of natural or acquired resistance enjoyed by the particular kind or group of cells and (2) on the maximum concentration which a given virus strain is capable of attaining. The first of these factors was suggested by the negligible damage to nerve cells in certain regions where virus was demonstrated in fairly high concentrations, such as in the olfactory bulbs and in certain regions in the brain traversed by the virus in its passage to the medulla and cord. It was, furthermore, suggested by the observation that in the cord the motor nerve cells, the most vulnerable of all nerve cells, seem to tolerate a concentration of virus up to a certain critical level, when they suddenly succumb in great numbers with a rapid onset of paralysis. Regarding the second factor, it is known that different strains of any virus may vary widely with reference to the maximum concentration

which they are able to build up individually, even under favorable conditions. One may speak of low titer and high titer strains. A strain of poliomyelitis virus which is unable to reach concentrations sufficiently high to inflict damage on the most vulnerable nerve cells, motor nerve cells, would, of course, not be able to induce a paralytic poliomyelitis. Such a strain may, nevertheless, effect extensive invasion of the nervous system. Naturally immunizing strains may be of this type and such a relationship can sometimes be identified in experimental animals,[48] one in which a virus, although able to invade the central nervous system from the brain to the lumbar cord, is presumably unable to increase in concentration to the point of inducing significant nerve cell damage and paralysis. Although the two general factors mentioned seem fairly obvious there are no doubt other factors, such as the effects of overexertion, chilling, etc., which also play a role in determining the final outcome of an infection.[49]

CLINICAL ASPECTS

Clinically the disease during its preparalytic stage or in its nonparalytic form continues to challenge the best diagnostic skill. There are no specific diagnostic aids to which the physician can turn for help. Raffel and Schultz[50] have recently reported extensive studies carried out in an endeavor to find a simple practical method for identifying either an existing infection or an acquired immunity to the disease. The results were entirely negative.

In the realm of treatment also there has been no important advancement. Serum therapy continues to be regarded as of doubtful value.[51] The possibilities of chemotherapy have been under investigation, but the results reported so far have been negative.[52] A claim for potassium chlorate[53] has not been supported by the results of subsequent workers;[54] those for vitamin C[55] have also failed confirmation,[56] while those which have been suggested for vitamin B_1[57] require the support of much more evidence to place them on a convincing basis.

The present status of orthopedic treatment and rehabilitation has recently been reviewed by Ober.[51]

IMMUNITY RELATIONSHIPS

Our knowledge of the immunity relationships in this disease has not changed greatly during the past few years. Natural resistance probably rests in part on inheritable differences in the protoplasmic constitution of nerve cells of different individuals and possibly also upon subsidiary constitutional factors. Acquired immunity seems to be related primarily to changes which have taken place in the protoplasm of normally susceptible nerve cells as the result of exposure to virus rather than upon the presence of circulating antibodies in the blood plasma.[58] Antibodies may indeed not always be demonstrable in association with an acquired immunity, though they frequently occur in varying amounts. When present, they have been regarded as purely secondary to the more fundamental protoplasmic change within the nerve cells, the result probably of an overflow of virus into the antibody producing reticuloendothelial system. On the basis of this assumption, they should not appear in the blood plasma, unless there has been infection of nerve cells from which such an overflow could occur. In other words, their presence in the blood should always be a testimony to the fact that a protoplasm modifying infection of neurones has occurred and that in consequence of this

a state of resistance to the disease has been established. This has, however, not been borne out by recent observations. Instances are now on record in which patients have presented antibodies in their blood at the time of onset of the disease.[59] Earlier surveys[51] had shown that a high per cent of adults, especially in urban communities, possessed antibodies for the virus in their blood and it was generally held that these persons had acquired immunity to the disease. This conclusion seems no longer to be justified and is rather contrary to the assumption that the infection responsible for the appearance of these antibodies had involved an invasion of nerve cells, at least in any significant degree. The observations at present would seem rather more in harmony with Burnet's view of an epitheliotropic virus infection, one in which the virus has in some way reached the antibody producing mechanism but not the nervous system, there to produce the cell modifying infection necessary to establish a true resistance to the disease. There are other possible explanations for this presence of antibody and absence of immunity which I cannot take the time to present.[60] But while the cell modifying effect of an infection seems essential for the induction of acquired resistance, it has become apparent that actual invasion of the nervous system is not always followed by a solid and lasting immunity. Instances of second attacks of paralytic poliomyelitis in man are on record.[51] In monkeys, too, a state of solid resistance does not always follow the paralytic disease as recent observations have shown, but such second infections, especially with homologous strains, are comparatively uncommon.[61]

PREVENTION

Regarding the prevention of this disease there is little that can be said. It is now generally known that both serums and vaccines have proved ineffective as prophylactic agents. Time does not permit me to develop the possible reasons for these failures nor to consider the possibilities of a solution in this direction. Of course, no one can say that some kind of vaccine may not yet be realized. Earlier I mentioned that the SK strain after adaptation to mice showed itself as much less pathogenic for monkeys. According to Jungeblut and Sanders,[7] it is possible to immunize monkeys to some extent against the more virulent monkey passage virus by means of the "murine" virus. Whether out of such observations will come the clue to a practical measure only time will tell.

A word regarding chemical prophylaxis. Although it has been established that certain chemical agents applied to the olfactory mucosa in monkeys are highly effective in preventing infection by the intranasal route,[62] such a measure, granting that it could be safely applied in man, would, of course, be applicable only if the virus commonly entered by the olfactory pathway. Until the natural portal of entry is definitely known and the pathogenesis of the disease is more clearly understood, it seems unlikely that a truly practical measure will suggest itself for the control of this disease.

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Round Table Discussion on Tuberculosis

Chairman: Fairfax Hall, M.D., New Rochelle, N. Y.

Associates: Edith M. Lincoln, M.D., New York, N. Y.
Clement A. Smith, M.D., Boston, Mass.
Chester A. Stewart, Ph.D., M.D., New Orleans, La.

Secretaries: Park J. White, M.D., St. Louis, Mo.
Reginald A. Higgons, M.D., Port Chester, N. Y.

Opening Discussion of Round Table on Contact Infection and Tuberculosis in Children

Fairfax Hall, M.D., New Rochelle, N. Y.

The Contact Infection Committee has been concerned with measures for preventing infection of children with diseases acquired from their adult associates.

Acute respiratory infections are the commonest. Too little can be done to protect children from this other than to avoid contact of children with adults in the infectious stage.

Syphilis is feared by many parents, especially when servants and nursemaids are employed. Children are unlikely to become infected by syphilitic adults except in rare instances, through kissing or sexual contact. F. R. Smith, Jr., of Baltimore was able to collect only 125 such cases after extensive search. Of course, it is best that a nursemaid have a Wassermann test. A negative Wassermann reaction, however, may give a family a false sense of security. It is safer to employ, for the care of a child, one who has a positive Wassermann and is being adequately treated.

Gonorrhea in an adult associate of children is dangerous, especially for girls. Pre-employment and infrequent examinations for its detection as a means of prevention are unsatisfactory.

Tuberculosis is the most dangerous disease to which children are exposed by adults. Early detection of this disease by x-ray of the lungs of adults offers an excellent means of protecting children from tuberculosis. Parents (and sometimes grandparents) are the most common source of tuberculosis infection for children. Nurses, teachers, janitors, and personnel of children's institutions must be considered as a possible source.

Although the presence of the tubercle bacillus in the environment is much less prevalent than formerly, it is still so widespread that approximately 25 per cent of high school seniors have a positive tuberculin reaction from a primary infection. Rejection from army service of the draft, because of tuberculosis, has been about 1 per cent.

We may not be impressed with the seriousness of a primary infection because progressive and fatal tuberculosis in childhood has become rare. However, few of us have the opportunity to follow a patient with a primary infection to the age where manifest tuberculosis of the reinfection stage occurs most often.

Tuberculosis is still a serious problem.

The pediatrician is public health minded. Prevention of disease is part of our daily routine. What shall we do about prevention of tuberculosis? We have with us three experts with a wide background of experience to discuss the practical aspects of tuberculosis prevention and other matters related to this disease in which you may be interested.

The Contact Infection Committee is very anxious to benefit by their advice. We all, as pediatricians, have this opportunity to clarify our ideas on tuberculosis.

The Control of Tuberculosis

Chester A. Stewart,* M.D., New Orleans

The control of tuberculosis, a highly contagious but preventable disease, is a problem that challenges our ingenuity. The greatest progress we have made in solving this problem relates particularly to the eradication of the disease from cattle.

Efforts to prevent tuberculosis in animals by immunization have been carried out for more than a half century. The investigators who were interested in this method of controlling the disease include Cavagnis (1886), Grancher (1889), Trudeau (1892), Pearson (1900), Von Behring (1901), Friedmann (1903), Calmette (1905), Klimmer (1906), Koch (1906), Raw (1906), Theobald Smith (1908), Arloings (1909), and Calmette and Guerin (1913). The antigens used by these investigators included virulent tubercle bacilli and avian and turtle bacilli as well as organisms whose virulence was attenuated by carbolated water, repeated culture, aging, passage through salamanders, etc. In addition bacilli killed by heat or by mixing them with chloral in an alkaline sugar solution were used.

About thirty-five years ago von Behring's bovovaccine was considered the triumphant solution of the tuberculosis problem in animals. Von Behring rated his preparation on a par with smallpox vaccine and spoke of the use of bovovaccine as "jennerization." But in time Von Behring's bovovaccine, Friedmann's turtle bacillus vaccine, Klimmer's antiphymatol, Koch's tauruman, and other preparations fell into disuse when increasing experience disclosed their failure to prevent tuberculosis. Recently the bacillus of Calmette and Guerin has received considerable attention but more time must elapse before final decisions relative to its effectiveness can be made. However, since fifty years of experimenting have failed to produce a dependable vaccine, it seems that immunization is not likely to solve our tuberculosis problem.

Programs for the control of tuberculosis by preventing infection began to appear about the time the experimenting with vaccines started. In 1891 Gutman of Russia and Bang of Denmark advocated separating the infected from the uninfected animals. Between 1900 and 1902 other plans for controlling the disease were devised which provided for the segregation of clinically ill cattle (Germany), the isolation of cows whose milk contained tubercle bacilli (England), or the use of healthy appearing cows for nursing calves (Sweden). In all of these programs an effort was made to preserve rather than to slaughter the tuberculous animals. The methods employed in Germany, England, and Sweden failed to use the tuberculin test for the identification of diseased animals, and in this respect they were inferior to the programs developed in Russia and Denmark.

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The method devised in Massachusetts in 1894 for the purpose of controlling bovine tuberculosis provided for the slaughter of all tuberculin sensitive cattle, and rigid standards for quarantine of the borders of the state. An elaboration of this method of tuberculosis control was made compulsory in the District of Columbia in 1909. This step marked the beginning of area testing in the United States and became the foundation for the comprehensive area testing plan which was adopted in 1917. The provisions of this program included the routine and repeated application of tuberculin tests to all cattle and required the slaughter of all infected animals. In addition, funds were appropriated to compensate farmers for the loss of condemned animals. Provision was also made for rating districts, counties, and states either as tuberculosis-free areas if no positive tuberculin reactors were present or as modified accredited areas if the incidence of tuberculin sensitivity was reduced to 0.5 per cent or less.

Six years after the comprehensive area testing program was adopted, seventeen scattered counties qualified as modified accredited areas, and in 1928 North Carolina became the first accredited state. Subsequently the number of accredited states increased to 3 in 1930, to 17 in 1935, to 47 in 1938 and to 48 in 1941. In the relatively brief span of twenty-four years, therefore, the incidence of infection with tubercle was reduced to one animal in 200 for the entire United States. This accomplishment is unquestionably the greatest demonstration of the successful control of a highly contagious disease recorded in history. Nothing comparable to this accomplishment has come from fifty years of experiments with vaccines.

Since bovine tuberculosis yielded very promptly when infection was prevented, it seems probable that human tuberculosis should yield to similar measures. The Contact Infection Committee has approved a tentative plan for preventing tuberculosis which includes the following procedures: (1) the periodic application of tuberculin tests; (2) complete examination of all tuberculin sensitive patients; and (3) the segregation of open cases until they cease to be communicable. This tentative plan has been submitted by the chairman of the Contact Infection Committee for study and revision. It is hoped that the American Academy of Pediatrics will devise and adopt an official program for the eradication of tuberculosis and will guide its entire membership in the vigorous application of this program.

Through assuming active leadership in this respect our organization can make a significant contribution to the control of tuberculosis. Promotion of this program on a comprehensive scale obviously requires the expenditure of large sums of money. But since $260,000.00 brought bovine tuberculosis under control, perhaps a few millions can be raised to help man put himself on a par with the cow with respect to tuberculosis.

In 1932 I started recommending the routine survey of each household unit that employed my professional services. During the initial survey that was made on those household groups, an initial test with 0.1 mg. of old tuberculin was administered to 2,159 children and to 2,090 adults. The initial survey of this entire group resulted in the discovery of thirty-four adults with clinical tuberculosis.

Follow-up studies extending over an average period of three years were made on 654 children and on 242 adults who reacted negative to the initial tuberculin test. During this period 2.6 per cent of the children and 14.5 per cent of the adults, who originally reacted negative to 0.1 mg. of old tuberculin, became sensitive to this dose of the material. Careful investigations were made in each instance where a newly acquired infection was disclosed and resulted in the discovery of fifteen additional patients with open pulmonary tuberculosis. This modest survey conducted in private practice resulted, therefore, in the detection of a total of forty-nine actual human sources of contagion. This limited experience prompts me to recommend that all physicians include a tuberculosis survey in the professional service they offer to their patients. A hundred thousand private programs conducted in

the private offices of the general practitioner and the specialists of the United States should result in the early discovery of hundreds of disseminators of tubercle bacilli whose detection would otherwise be overlooked or deferred.

In conclusion I recommend that the American Academy of Pediatrics adopt an official program for the eradication of human tuberculosis and also guide the entire membership of the organization in the application of the officially approved program. If the Academy assumes the position of leadership, its campaign should soon attract national and international interest and support. This endeavor can lay the foundation for the adoption of an official antituberculosis program by our central organization, the American Medical Association. And when we have enlisted the united effort of the American Medical Association in vigorously promoting an officially approved antituberculosis campaign, human tuberculosis probably will parallel bovine tuberculosis in yielding to measures that prevent infection with virulent tubercle bacilli.

Observations on Childhood Tuberculosis

Edith M. Lincoln, M.D., New York

Dr. Stewart has talked about the prevention of tuberculosis. That is an ideal which may some day be accomplished by the means he suggests. In the meantime, since it is unlikely that we can at once segregate all infectious cases effectively, we shall continue to see cases of tuberculosis in its early stages, the so-called primary tuberculosis. Some of these patients will die, the number depending partly on the extent and length of exposure and the resultant amount of tuberculosis. In some parts of the country there will be more survivors than in other sections. In Minnesota a recent report by Tortone and others from Lymanhurst listed the deaths from primary tuberculosis for children under 6 years of age as 5.8 per cent of the total number with evidences of primary tuberculosis. At Bellevue Hospital in New York City over a period of ten years 20 per cent of the children with x-ray evidence of uncalcified primary tuberculosis died of the disease within a year.

Our problem of the prevention of contagious tuberculosis lies not with these unfortunates who die but with the survivors and particularly with those who had a large amount of the disease and still survived. For we believe that not only does heavy infection influence the prognosis for life but also for later complications.

The pathogenesis of chronic pulmonary tuberculosis, which is by all odds the form most dreaded from the point of view of contagion, is not definitely known. But all the evidence we have been able to gather over a period of more than twenty years at Bellevue Hospital indicates that whereas re-exposure to tuberculosis may play a part in causing active disease in some individuals, in the great majority of cases chronic pulmonary tuberculosis is just a late complication of the first attack of the disease. We have repeatedly seen cases develop when the original contact has been removed for a long time and no new source case could be found. Many children are frequently re-exposed throughout childhood to a parent with open tuberculosis and yet either never develop the disease nor show evidence of it for years. The exogenous reinfection theory does not explain why chronic pulmonary tuberculosis is usually in the upper parts of the lungs, whereas most primary foci which are known to be of exogenous origin are found in the middle and lower thirds of the lungs. Nor does this reinfection theory shed any light on why the peak of occurrence of chronic pulmonary tuberculosis is so much earlier in girls than in boys. Until this problem of the relation of sexual maturity to the development of chronic pulmonary tuberculosis is solved, we possess no means of preventing tuberculosis at adolescence. In the meantime we must try to find minimal cases before they become contagious. We believe this can best be done by following with chest x-rays children who have had primary tuberculosis and adolescents who develop positive tuberculin tests regardless of whether or not the primary lesions are visualized on x-ray.

The question always arises in a follow-up survey whether in order to find most of the cases it is necessary to include all children who have ever had positive tuberculin tests even if chest x-rays have always been negative. Since it seemed likely from our evidence that there was a direct correlation between the extent of the original infection and the prognosis of the disease tuberculosis, it seemed possible to me that the degree of the primary tuberculosis might also determine the occurrence of complications in later life, chiefly chronic pulmonary tuberculosis. Because of this theory I began in 1930 to follow a group of consecutive cases of primary pulmonary tuberculosis from our Children's Chest Service. Over 90 per cent of these cases were first found by the usual case-finding methods, history of exposure to a case of tuberculosis, tuberculin test done as a routine or by chest x-ray made as part of a routine examination. The group includes 600 patients with pulmonary primary tuberculosis with involvement of nodes or parenchyma, or both, 357 patients with calcifying or calcified primary pulmonary tuberculosis, and 43 infants infected with tubercle bacilli as proved by tuberculin tests but with negative chest x-rays. The mortality of this group within a year from primary tuberculosis was 20.6 per cent. The infants naturally had a much higher mortality rate than the total group, but it is interesting to note that whereas the mortality in the group of infants with x-ray evidence of primary tuberculosis was over 30 per cent, the rate for the small group who had negative x-rays and presumably small primaries was only 5 per cent. It is probable that the difference in size of primaries may result in part from smaller dosage and may reflect a shorter or less intensive exposure to the source case. If this theory is correct, we should expect a higher dosage and higher mortality in tuberculous children in localities where crowded living conditions exist, and this may explain the difference in mortality statistics in various parts of the country.

We are at present following 420 survivors of the original group of children with active primary tuberculosis and 320 survivors of those first seen with healing lesion. One-half of the entire group of 740 children is still under 10 years old, but already 5 per cent of the total group, or 36 children, have developed chronic pulmonary tuberculosis. Although there were about equal numbers of boys and girls in the original group, 25 girls and only 11 boys have developed chronic pulmonary tuberculosis. The average age of onset was 13 years and 3 months with an age range of 5 to 19. Most of the cases were minimal when first found, but treatment was often delayed by the patients due to the absence of signs and symptoms. The mortality in the group so far has been 19.5 per cent. In contrast to this we have a much larger group of children who had chronic pulmonary tuberculosis when first admitted to our service. The same disproportion in numbers of males and females exists in this group, but 57 per cent of them were far advanced when first seen and 41 per cent have already died, a mortality rate more than twice that of the cases found by follow-up. The time interval between the development of the primary infection and of chronic pulmonary tuberculosis is of great interest. Regardless of the age of infection the tendency is for the chronic pulmonary tuberculosis to manifest itself around adolescence. Thus a child who had a primary tuberculosis at 2 years of age will usually not develop chronic pulmonary tuberculosis for many years, if at all, whereas an adolescent may have chronic pulmonary tuberculosis develop immediately after a primary. The long interval may explain the infrequency of discovering chronic pulmonary tuberculosis at adolescence in children who have been observed for years with a positive tuberculin test as the only evidence of tuberculosis. In a group of cases in our own as well as in the cardiac and other follow-up clinics, we have seen only three cases of chronic pulmonary tuberculosis develop at adolescence in children known to have had positive tuberculin tests for years but without roentgen evidence of primary tuberculosis. In two of these cases a marked nontuberculous suppurative disease of the lung apparently precipitated the development of chronic pulmonary tuberculosis.

Therefore from our experience at Bellevue I believe that the great majority of cases of chronic pulmonary tuberculosis occurring in children and adolescents will be diagnosed early before they are in a contagious stage if following routine tuberculin tests we regularly follow all children who have had primary tuberculosis which could be visualized on x-ray or whose positive tuberculin tests develops near adolescence or later. I think Dr. Stewart's plan of following all children with positive tests should remain the ideal, but when it is not possible to carry it out in full, selection of the cases I have suggested for follow-up until the age of 25 years will, I believe, uncover most cases of chronic pulmonary tuberculosis occurring in adolescence and early adult life.

The Control of Childhood Tuberculosis in Massachusetts

Clement A. Smith, M.D., Boston

About two years ago a joint committee was formed to represent the local members of the American Academy of Pediatrics and those of the New England Pediatric Society for investigating the control of contact infections dangerous to children. That committee began its work by sending questionnaires to about twenty Massachusetts physicians engaged actively in the practice of pediatrics, since their experience and advice might indicate the scope of the problem and the limitations of an effective plan.

For reasons which scarcely need presenting, it became clear that attempts to prevent childhood venereal disease by the periodic examination of household employees would be unsuccessful. It was also evident that little could be done to prevent typhoid fever by such methods, nor was it reasonable to suppose that common respiratory infections among children could be diminished by any feasible scheme of regulating household contacts. The problem narrowed itself down to deciding what should be done about the tuberculosis hazard.

That some appraisal should be made as to the need for a special campaign against this disease or the incorporation of a new case-finding bureau was indicated by the trend of tuberculosis mortality in this region. Whereas, for example, more than 200 infants succumbed to tuberculosis in Massachusetts during the year 1920, 72 died in 1930, and only 19 in 1940. In other words, with the exceedingly effective organizations already operating among us, the amount of infantile tuberculosis has been cut to about 10 per cent of what it was only twenty years ago. Since our influence in a campaign for the systematic examination of domestic servants and other household adults would obviously find its largest application in that economic class of families whose children are seen by private pediatricians, we were especially interested in the amount of morbidity and mortality which had occurred in the past experience of the pediatricians answering the questionnaire. Among twenty-one replies, eleven doctors stated that to the best of their knowledge no tuberculosis traceable to servants, nurses, or school teachers had ever appeared in the families under their care. The other ten pediatricians had known of seventeen instances of tuberculosis conveyed to children in this fashion, and four deaths had resulted therefrom. It must be admitted that unsuspected infection may have occurred which would swell these figures, but the total number could not have been very large when one considers the total state figures.

The results of this survey, plus the state-wide evidences of careful work by the public health institutions, led the committee to report against any formal campaign for a central office or clinic for the certification of domestic workers. We were influenced in this decision also by the fact that the Massachusetts Tuberculosis League had been actively engaged in working toward municipal laws for the examination of school teachers in Massachusetts cities and is at the moment also campaigning for the roentgenologic examination of all women coming to obstetric hospitals. There seemed to be plenty of agencies already functioning to care for the added

load of certifying household workers roentgenologically if the agencies were willing to assume that undertaking. It seemed also that practicing pediatricians acting as medical advisors to a large number of families (probably to the majority of those able to pay for domestic help) might with some encouragement arrange for the servants of these families to be x-rayed. Therefore, we are now in the process of inquiring from the various tuberculosis sanitoria, consultation clinics, and diagnostic clinics in the urban sections of the state whether (and for what fee) they will admit domestic workers for roentgenologic examination. The response is almost unanimously affirmative and indicates the willingness of these organizations to participate (usually without charge) and their sense of the desirability of the project.

It is hoped that this will make possible the publication of a list of clinic places and times which can be sent to all pediatricians in the state as well as to such other physicians as may use it. Specific instructions then can be given to families as to where their domestic workers may go for this roentgenologic certification. In most cases a letter from the family pediatrician or other physician will, quite properly, be required.

Besides this brief description of a plan for safeguarding household contacts of children, I should like just a moment to touch upon certain phases of the problem that have interested us.

1. We consider smaller children, and especially infants under 2 years, to be those mainly in need of protection. Tuberculous processes in children between the ages of 7 and 14 years have, in our experience, been so benign as to make any expensive plans for such children of dubious value.

2. The dangers to infants may come from unsuspected directions. Dr. Pope is to publish shortly[1] an account of a recent outbreak of tuberculosis disseminated by a graduate nurse taking care of newborn infants in a reputable general hospital not far from Boston. The state health department has been most industrious in seeking out and testing the newborn infants who were cared for by this nurse. Twenty-six of 426 tested are tuberculin-positive. Five of these 26 have roentgenologic evidence of tuberculosis and two others have died of the disease. In how many hospitals known to us would this epidemic have been prevented by a routine annual roentgenogram of every nurse employed? How many of us have our own lungs annually certified?

3. A roentgenogram may not be actually essential for these examinations of adults in contact with children. The experience of the Metropolitan Life Insurance Company[2] is extremely interesting. That company has for several years used fluoroscopy as an examination method in case-finding among applicants for employment. Over 25,000 persons have been examined and fluoroscopy has been found sufficiently accurate for detecting pulmonary tuberculosis in this large group. About 1 per cent of these applicants, most of them young adult or late adolescent females, have been discovered to be tuberculous, usually to a comparatively minor degree. One more point of interest is that whereas clinically significant tuberculosis has appeared in about 1 per cent of the applicants for employment, annual examination of employees has revealed new tuberculosis infections in only about 0.1 per cent.[3]

To summarize, it is suggested that fluoroscopy might take the place of film-taking in examination of adults, that about 1 applicant in 100 might be expected to show some evidences of tuberculosis, that tuberculosis may be spread in other places than homes and schools, and, finally, that the existing public health organizations may be adequate (if given our support) to solve the problem of household exposure of children to tuberculosis.

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Discussion of Tuberculosis Survey on 215 Families

Fairfax Hall, M.D., New Rochelle, N. Y.

All these families are private patients with children attended by a pediatrician.

The adults have had better than average medical and obstetric care. This has already excluded all obvious and advanced cases of active tuberculosis. Very few, however, had ever had a lung x-ray. Almost none had ever been tuberculin-tested. The great majority of mothers were agreeable to a tuberculin test at the same time it was given to their children. The few objections were chiefly because of fear that a positive test would cause worry. Some were enthusiastic and asked why it had not been done before.

Fathers were inclined to be cooperative but harder to get to the pediatrician's office. Domestics were cooperative when the family was tested.

TABLE I

TUBERCULOSIS SURVEY OF 215 FAMILIES

	TOTAL NO.	NEGATIVE TUBERCULIN	POSITIVE TUBERCULIN (%)	LUNG X-RAY	X-RAY POSITIVE REACTION (%)
Mothers	215	52	163-75.8	73	44
Fathers	55	13	42-76.3	16	38
Domestics	27	11	16-59.3	5	31
Relatives	7	2	5-71	0	0
Total adults	304	78	226-74.3	94	41.6
Children	298	273	25-9	22	88

X-RAY FINDINGS IN NINETY-FOUR ADULTS

Primary Tuberculosis, 91-96.8 per cent; Reinfection Tuberculosis, 3-3.2 per cent

NO X-RAY PATHOLOGY	CALCIFICATION SMALL AREAS	CALCIFICATION EXTENSIVE	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED
10	68	13	3	0	0
		16 Clinically significant	17%		

TOTAL ADULTS	NO TUBERCULOSIS	PRIMARY TUBERCULOSIS	REINFECTION T. B.
304	78-25.7%	219-72%	7-2.3%
		Number to be expected if X-ray findings same proportion as for 94 reported above.	

Tuberculin tests were mostly Mantoux 0.05 c.c. of 1-1000. No serious or sloughing reactions occurred. Mothers were tested above the knee because reaction disfigures a bare arm. Some complained of soreness. The patch test is useful to avoid this. A few became unduely alarmed by a positive reaction. This anxiety subsided after obtaining a lung x-ray. A positive tuberculin reaction is the greatest incentive toward getting a lung x-ray.[42] Many could not get to a radiologist soon enough.

Need for low cost x-ray is evident.

Reading films requires a real expert, the best being one experienced in clinical tuberculosis.

Findings are of interest and of value. A number of adults were found with tuberculosis of clinical significance which is in need of follow-up.[16]

Proportion of reinfection tuberculosis was about the same as other surveys of a similar age group. No cases of active open tuberculosis were found.

Education value in regard to tuberculosis prevention was a feature of this survey.

All reports of x-rays were given to these adults for them to pass on to their own physicians.

This family survey seems a proper one for the pediatrician to conduct among his own patients.

Private patients are entitled to as good, and better, medical care than the patients who attend clinics.

DISCUSSION

DR. LINCOLN.—Dr. Smith, do you do routine tuberculin tests on ward patients?

DR. SMITH.—Yes. Seven per cent were positive at 12 years of age, 14 or 15 per cent in adolescents.

DR. LINCOLN.—For some reason the incidence in Massachusetts seems to be half that in New York. Both have a falling death rate. Of babies under 2 years of age in New York City in 1930, 157 died of tuberculosis as compared with 56 in the year 1939. Yet during the years 1930—1939 in one clinic in New York City I saw 600 cases of primary tuberculosis with a mortality of 20 per cent, most of them autopsied.

DR. J. C. OVERALL, NASHVILLE, TENN.—Dr. Lincoln, are children hospitalized in separate institutions?

DR. LINCOLN.—Yes, at Seaview or Seton. We do not believe in sending children to institutions unless the care at home is sure to be inadequate.

DR. H. C. THOMPSON, JR., TUCSON, ARIZ.—Is there danger in having children with primary tuberculosis kept at home with noninfected siblings?

DR. LINCOLN.—Yes. Stomach washings of infected children should be examined as a precaution.

DR. STEWART.—Do you not agree that primary tuberculosis in children is usually unimportant as a source of infection?

DR. LINCOLN.—Yes, but if there is much cough, that should make one presuppose greater infectivity.

CHAIRMAN HALL.—Yet we must bear in mind the Swedish reports of early primary cases with positive stomach washings.

DR. STEWART.—It is very hard and probably unnecessary to isolate primary cases. It is the patients who develop later active tuberculosis who are dangerous.

DR. SMITH.—It takes a great many examinations of stomach washings to give reliable results.

DR. LINCOLN.—I agree. The first morning specimen is most important.

CHAIRMAN HALL.—Let us have some discussion of Dr. Stewart's "Ideal Plan."

DR. A. G. JACOBS, MEMPHIS, TENN.—Is a flat x-ray plate sufficient? Also, how important is the lateral plate?

DR. STEWART.—Ideally, stereoscopic and lateral plates should be made, but practically a flat plate which can be more readily repeated is adequate. For years I have used paper films.

DR. P. J. WHITE, ST. LOUIS.—Do you not think that even a paper film is to be preferred to fluoroscopic examination alone?

DR. STEWART.—Yes, but it is most important that we should all be doing something.

DR. OVERALL.—I have been carrying out the "Ideal Program" for some years. Up to the past three or four years it has been hard to get private patients to permit tuberculin tests. How often should we repeat x-ray examinations of children with positive tests and plates? In a survey of schools in Nashville, 15 per cent of the children were found positive and all the positive reactors were x-rayed. Three active cases were found.

DR. STEWART.—At Lymanhurst we x-rayed everyone at least annually. Positive reactors should be x-rayed at least that often.

DR. LINCOLN.—In New York, after the lesions have calcified, the department of health does not x-ray them again until the age of 10 or 12 years. Annually would be better.

DR. E. W. BARRON, BOSTON.—At Floating Hospital we found 120 children with positive tuberculin tests and took routine x-ray pictures every six months.

DR. J. I. LINDE, NEW HAVEN.—I should like to stress the public health aspects of this subject, including the cost. Case-finding is expensive. But its educational value is very great. We x-ray nurses of our Visiting Nurse Association, also the workers at the Children's Community Center. We find Powers films satisfactory. I am on the State Tuberculosis Commission from which we get excellent cooperation. With the portable Westinghouse apparatus we have found 1 per cent of the draftees positive. With the Kelly-Koett machine we have taken 25,000 pictures. We can take as many as 300 a day. We have not extended case-finding to industrial groups yet. In New Haven if a patient cannot pay for his x-ray examination, the health department pays part of the cost. Even so, only 60 per cent of our contacts are x-rayed.

CHAIRMAN HALL.—Dr Linde, what are the criteria for rejection of draftees?

DR. LINDE.—The pictures are examined at the various state sanatoria whose roentgenologists report back. We have a director of case-finding, Dr. Paul Phelps.

DR. THOMPSON.—In Arizona any case with a suspicion of positive findings is rejected.

DR. LINDE.—I have asked the Public Health Committee of the state medical society to review the case-finding activities of the State Tuberculosis Commission.

DR. C. C. PAYNE, DAYTON, OHIO.—How many children of those in your family survey contract tuberculosis from sources outside the home and school?

CHAIRMAN HALL.—Not very many. One patient picked it up from a neighbor.

DR. F. C. MCDONALD, BOSTON.—Grandparents must not be neglected as sources of infection. That age group, the third "peak of mortality," must be carefully watched. Also, I should like to mention the case of a negro family whose child was definitely shown to have contracted tuberculosis by moving into a room formerly occupied by a woman who died of the disease.

DR. STEWART.—Dr. Hall, may we have a show of hands indicating how many of those present favor the later adoption by the Academy of a program such as has been recommended. (There was but one dissenting vote.)

DR. R. C. BOND, WHEELING, W. VA.—I am not really dissenting, but I do prefer to send the adult members of the families I treat to their own physicians for testing. Our health department is very active in this work and cooperates well in testing those who cannot pay.

DR. STEWART.—We must all remember that we are responsible for our patients' environment.

QUESTION.—What is the percentage of positive tests among preschool children?

DR. STEWART.—Less than 5 per cent for children under 5 years of age in Minnesota. We must emphasize that tuberculosis spreads fastest in the adolescence, which is the kissing age.

DR. WHITE.—A community like Minneapolis, thanks to an institution like Lymanhurst, is tuberculosis-minded, with the result that many persons ask that the tests be made. Incidentally, I should like to call the attention of this group to the excellent program now operative at our Children's Hospital in St. Louis for the preliminary and periodic examination of staff members and hospital employees.

DR. STEWART.—In carrying out the program recommended we may lose a few families, but its educational value will doubtless gain us patients later on.

DR. SMITH.—In many communities, annual re-x-raying is not financially practicable.

DR. STEWART.—Sometimes insurance companies and other organizations may and do provide unexpected sources of support. At Lymanhurst the films themselves cost fourteen cents each, overhead bringing them up to seventy-five cents.

DR. WHITE.—I think we should be grateful to Dr. Lincoln for putting some fear into us by showing what may happen to patients whose early tuberculosis is overlooked.

DR. F. H. VON HOFE, EAST ORANGE, N. J.—At what age should we begin testing patients?

DR. STEWART.—At any age, usually from 9 months on. In private practice, performing the tuberculin test at the same time as the Schick test is satisfactory.

DR. R. P. ROGERS, WARREN, OHIO.—We are getting the program started in our county. Two hospitals are doing x-rays on the indigent. Ordinary films must be used. What do you consider the proper charge?

DR. LINDE.—A hospital charge of $1.00 per film is about cost.

DR. WHITE.—Some hospitals cannot or will not do it for so low a fee.

CHAIRMAN HALL.—Dr. Lincoln, would you close our discussion by giving us your ideas on the care of children with primary tuberculosis?

DR. LINCOLN.—Among our infants there was a 5 per cent mortality, mainly from tuberculous meningitis. With regard to treatment each case must, of course, be individualized. I have no new suggestions with regard to treatment. Adequate rest, food, and supervision remain the essentials. I have not found the sedimentation rate of real value in prognosis. Finally, remember that we should never use the term benign in connection with tuberculosis.

DR. SMITH.—The method of handling a positive reactor to tuberculin in young children at Children's Hospital, Boston, is as follows: If a child can be kept alive for one year after discovery, he will very probably be alive at 12 years. He should have very careful treatment during the first infection year; after this only occasional follow-up to 12 years; then x-ray examination and a discharge to the board of health clinic which follow him with annual x-ray during adolescence. Is this sufficient?

DR. LINCOLN.—Patients should be followed to 25 years of age as few break down after 25. About 90 per cent of all those who will die eventully will die during the first year of infection; therefore the follow-up between one-year post infection and adolescence may be less intensive with relative safety. Should any medical complication occur, the child should be surveyed again by the tuberculosis clinic before instituting other treatments.

DR. STEWART.—Tuberculin-test the children; then concentrate particularly upon the adult contacts. All tuberculin tested to save expense and only positive reactors x-rayed. These should be restudied ideally more often than once a year, but at least once a year. All negative reactors in intimate contact with positive reactors should be retested as frequently as possible. Any change in a contact's reaction to tuberculin suggests a breakdown in the supposedly sealed original case. Any compromise in a preventive campaign will certainly result in less than eradication of this disease.

DR. J. M. HIGGINS, SAYRE, PA.—Just what is the significance of a positive tuberculin test in an adult and in a child?

DR. STEWART.—The test means the same thing at any age. Any positive test means at least a primary tuberculosis lesion, but only clinical laboratory and x-ray studies will determine whether or not the disease has progressed past the primary stage. Also, if a test has been known to be negative to a certain date and then becomes positive, it helps in determining the time of infection.

DR. HIGGINS.—Does degree of reaction to test have any significance?

DR. LINCOLN.—There is no definite relationship to size or type of lesion. A test becoming less and less positive as time goes on, until finally giving a negative result, suggests final destruction of all tubercle bacillus in that patient's body.

DR. STEWART.—I feel that the larger size reactions may occur nearer to the date of active infection. I have thought that a strong reactor may be more susceptible to a new dose of infection.

DR. HIGGINS.—Should positive tests be repeated?

DR. LINCOLN.—They should not be repeated because of danger of severe focal reaction with flare-up of some focus of infection.

DR. HIGGINS.—Is it inadvisable to do a tuberculin in a child acutely ill from unknown cause?

DR. LINCOLN.—You may get a negative test during an acute infection with high fever.

DR. HIGGINS.—Assuming that a child has a positive reaction and a negative x-ray, should any other specific procedures be done for diagnosis?

DR. STEWART.—In an animal who is inoculated with tubercle bacillus you can almost immediately recover the tubercle bacillus from many parts of the body. The same must apply to human beings. There must be tubercle bacillus in many parts of the body other than the visible primary complex in lung. These other seedlings may never cause obvious disease.

DR. HIGGINS.—Is there a choice between P.P.D. and O.T.?

DR. LINCOLN.—A solution of P.P.D. is not stabile for more than forty-eight hours, whereas an O.T. solution is much more stable and probably is efficiently active up to six months and probably much longer. This saves expense.

DR. W. E. NELSON, PHILADELPHIA, PA.—Have the time elements been studied in the P.P.D. solution?

DR. HALL.—Good advice seems to indicate that it is not as stabile as O.T. solution. What about the patch test?

DR. SMITH.—It is a good test if checked by O.T. in suspicious cases who have negative patch test. In our experience the patch test is about 97 per cent accurate. It may give rather severe local reaction at times.

DR. C. L. LAMAR, BIRMINGHAM, ALA.—How long will a really positive test be readable?

DR. STEWART.—Probably o. k. to read it in one week, certainly in seventy-two hours. A positive test must be indurated as well as discolored.

DR. LAMAR.—Is a first infection ever an asset if sealed off?

DR. STEWART.—In spite of natural acquired immunity which the race should develop throughout the centuries, the disease still causes appreciable percentage of all human deaths. There is no effective immunity. No vaccination has yet solved the problem. I do not believe in immunity to tuberculosis. The needles and syringe should not be used for other tests because the material is difficult to remove completely.

DR. DAVID KLEIN, MONTREAL.—What is your experience with the tuberculin test in allergic children with eczema, etc?

DR. LINCOLN.—The skin is more sensitive but the test is still of the same significance. These children do react atypically to the patch test at times.

DR. KLEIN.—Do you have any arbitrary rules regarding amount of O.T. injected?

DR. LINCOLN.—We consider no child negative unless not reactive to 1 mg. of O.T.

DR. NELSON.—Do large amounts of O.T. give false positive reactions?

DR. LINCOLN.—No, but large amounts of material injected may cause a local foreign body reaction of transient character.

DR. STEWART.—It might be wise to read the tests in seventy-two hours and insist upon some induration. In any case, the errors will be a very unimportant small percentage.

DR. HALL.—What about delayed reactions to the patch test?

DR. STEWART.—No experience.

DR. HALL.—Should the Contact Infection Committee recommend the family survey plan of Dr. Stewart and Dr. Hall to the American Academy of Pediatrics for a National program? (There was a unanimous show of hands).

DR. KLEIN.—People should be fully advised as to the true significance of the tuberculin test so as not to frighten them too much.

DR. LAMAR.—Should not all nurses in hospitals and children's institutions be examined periodically by x-ray?

DR. HALL.—Much is being done toward that already.

DR. LINCOLN.—At Bellevue all employees are required to be x-rayed every six months. One charge nurse was missed and she infected several infants.

DR. SMITH.—Would the patch test be satisfactory in screening families?

DR. STEWART.—Any test should be encouraged without restriction so as to avoid as much dissenting opinion as possible, although I prefer Mantoux.

DR. NELSON.—How about cheap small x-ray films?

DR. HALL.—The 4 × 5 inch x-ray plate cost only about seven cents and the machines cost approximately $2,000.00 for a stationary and $6,000.00 for a mobile unit. These should be used more widely.

DR. LAMAR.—If only 1 in 3,000 young children show positive x-ray, would it not be wiser to test only young children and x-ray only those near puberty?

DR. STEWART.—It might be permissible if expense is prohibitive because the danger is less during latter half of first decade.

DR. LINCOLN.—You would miss the chance of picking up early reinfection.

DR. SMITH.—Should positive reactors who are not really acutely ill be institutionalized to prevent later reinfection type?

DR. STEWART.—Money now available should be saved for institutionalizing the infective type unless removal of patient from contact in home warrants use of institution.

DR. LINCOLN.—Preventorium is of no value in preventing later breakdowns.

DR. HALL.—How important is it to remove the reactor from source of infection?

DR. STEWART.—Exogenous reinfection must play a part in breakdowns and therefore re-exposure is to be avoided.

DR. LINCOLN.—Every child should be removed from source as soon as possible. I agree with Wallgren that in most cases reinfection organisms are usually destroyed by a previously infected person who is already allergic to tuberculin.

DR. SMITH.—I agree with Dr. Lincoln and we see less fatal results in those cases coming to the hospital from houses without active foci of infection.

DR. HALL.—What is the optimum age to develop the primary lesion?

DR. LINCOLN.—The ages between 6 and 9 years in girls and 6 and 12 in boys. However, I would postpone it indefinitely if I could.

DR. SMITH.—We know too little about the older age groups now. As more people reach adult life without primary infection, we may learn something more about it.

QUESTION.—Describe primary tuberculosis.

DR. LINCOLN.—The disease should be considered as an infection which has complications occurring at various times after the infection.

DR. STEWART.—Tuberculosis goes through two phases of development: (1) primary stage and (2) some form of secondary disease occurring at some variable later date. If we had no phase other than the primary, the disease would be as mild as chickenpox and very little more dangerous. It is the later complicating breakdowns, no matter what time interval elapses, that is the dangerous stage of the disease.

DR. STEWART.—A positive tuberculin test indicates an actively living tubercle bacillus in the body although it may not be causing any active disease demonstrable at that particular time.

In Memoriam

KENNETH DANIEL BLACKFAN
1883-1941

Kenneth D. Blackfan, Thomas Morgan Rotch Professor of Pediatrics at the Harvard Medical School, died Nov. 29, 1941, at Louisville, Ky. He had undergone a serious operation last spring and was taking a sabbatical year from his teaching and administrative duties. He had planned to spend the winter in the south and was visiting in Louisville en route.

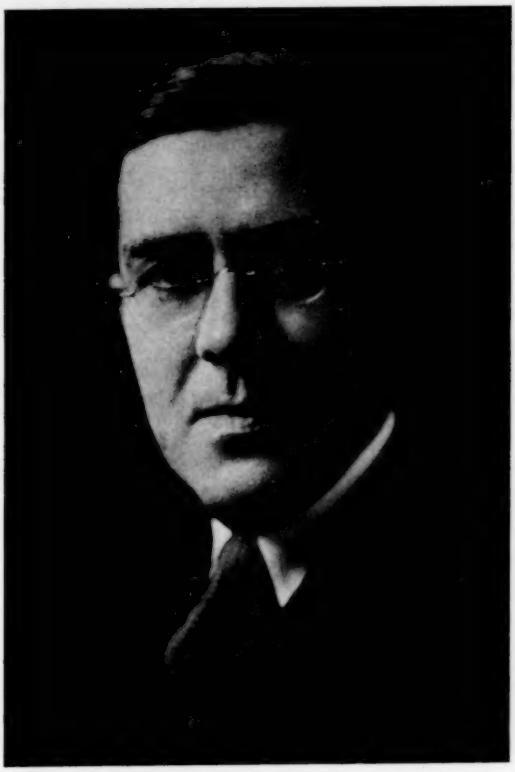
Dr. Blackfan was born at Cambridge, N. Y., Sept. 9, 1883, and was the son of Dr. Henry S. Blackfan, who practiced at Cambridge many years. He matriculated at Albany Medical College in 1901 and graduated at the head of his class in 1905, receiving the M.D. degree before he had reached his twenty-second birthday. The year following his graduation was spent in pathology and bacteriology at the Bender Laboratory and the Albany Hospital, and he then became associated with his father.

In 1908 he decided on pediatrics as a career rather than continue in practice and went to work under S. McC. Hamill at the Policlinic Hospital in Philadelphia. In the fall of 1911 he went to St. Louis with John Howland to become Assistant in Pediatrics in the newly reorganized Washington University School of Medicine, and Resident at the St. Louis Children's Hospital. After a year in St. Louis he went with Howland to Baltimore as Resident at the Harriet Lane Home and Instructor in Pediatrics at the Johns Hopkins Medical School, in 1917 was promoted to Associate, and in 1919 to Assistant Professor. In 1920 he was called to the professorship of pediatrics at the College of Medicine of the University of Cincinnati where he remained for three years. In 1923 came the call to the chair of pediatrics at the Harvard Medical School. During his eighteen years at Boston he gathered under his leadership a group of associates and younger men which has made the Harvard Clinic regarded by many as the leading pediatric clinic in the United States.

Among the societies to which Dr. Blackfan belonged were the American Pediatric Society, on whose Council he served from 1926-1933 and was president in 1938, the Association of American Physicians, the American Academy of Pediatrics, and the Society for Clinical Investigation. He was a corresponding member of the British Pediatric Association, and the Pediatric Section of the Royal Society of Medicine of England. From 1933-1935 he served on the Council of Pharmacy of the American Medical Association. In 1932 he was a delegate to the Berlin meeting of the International Committee on Nutrition sponsored by the League of Nations. As chairman of the Committee on Growth and Development of the Medical Section of the Third White House Conference held in 1931, he edited the four-volume report which has become the standard text for graduate students in pediatrics. In conjunction with his professorial position at Harvard he was Director of the Infants Hospital and Chief of the Medical Service at the Boston Children's Hospital. In 1932 when THE JOURNAL OF PEDIATRICS was founded he was appointed to the editorial board and was always active in determining Journal policies and in the selection of manuscripts for publication.

Many other items might be added, but the above record of his medical life shows two things very clearly: First, the position he deservedly established

for himself as one of the outstanding pediatricians of his time; and second, the respect in which he was held not only by pediatricians but also by the entire medical profession.



KENNETH DANIEL BLACKFAN

From the first he held to a high medical idealism, despite the fact that his early years were at times most discouraging. He was one of the very few who entered pediatrics over thirty years ago who did not have at least a part of his training in European clinics. Throughout his life he contributed much to medical progress. He was chiefly interested in clinical medicine, clinical investigation, and teaching. In his early years his work on hydrocephalus and in later years that on the blood dyscrasias were among his most important contributions. An *Atlas of the Blood in Childhood* by Blackfan and his associate, Louis Diamond, is now in press and will be published shortly. Perhaps even more important in a sense was his interest and stimulating influence on the investigative work of others under him to whom he always gave full credit. He had very definite ideas and ideals of his university position and held that teaching was his primary function. He was loved and respected by his students who affectionately called him "The Little Giant." One of his associates once said that a member of his staff might have to wait several days to talk a matter over with him but that he was always available to the student with a trouble or a problem. He was asked to assume greater uni-

versity administrative duties at one time but preferred to continue in his pediatric work. Not only in the medical school but by his many friends throughout the country was his advice being constantly sought on all kinds of medical problems.

Although a quiet, unassuming man, Dr. Blackfan had a force and determination that all of his friends and associates knew well. Perhaps a certain persistency or determination and thoroughness, together with an ability for strenuous work, were the most outstanding of his mental traits. This not only carried him through a discouraging early period when he was entering pediatrics but through a series of severe physical illnesses and resulting handicaps which would have overwhelmed most men with less strength of character. He demanded much of those associated with him but gave of himself equally. To those who knew him well there was a kindness and affection in his character that could always be depended upon. His death leaves a void in American pediatrics which no one will ever completely fill. His influence however will live for many years as he left a definite impress on the lives of hundreds of young medical men which will never be forgotten.

He is survived by his mother, his wife, Lulie Anderson Bridges of Louisville, Ky., whom he married in 1920, and a stepson, Turner Bridges. His family and home life was ideal. Those who had the privilege of visiting him at his simple summer camp near Cambridge where he spent his summers hold a memory of him they will always cherish.

Academy News

The following have been elected to Fellowship:

Dr. Morris L. Bridgeman, Portland, Ore.
Dr. John Thomas Leslie, Griffin, Ga.
Dr. Philip A. Mulherin, Augusta, Ga.
Dr. Edwin H. Rohlfing, St. Louis, Mo.

News and Notes

Dr. Harvey F. Garrison, Sr., of Jackson, Miss., was elected president of the Southern Medical Association at the annual meeting in St. Louis in November and will be installed as president at the meeting in Richmond next year. Dr. Garrison has been a former president of the Mississippi State Medical Society and State Pediatric Society and is state chairman of the Academy from Mississippi.

The following method of enlisting the interest of parents and teachers in the health of young school children has been worked out in Philadelphia and has been so successful that it is of general interest to all members of the Academy.

As State Chairman, of the Committee for Cooperation with Non-Medical Groups of the American Academy of Pediatrics, Dr. E. L. Noone worked out a plan for cooperation of the school systems and parent-teacher organizations of the Philadelphia area with a group of prominent pediatricians in a series of panel discussion meetings held in eleven selected schools in and near Philadelphia. In the several meetings there were presentations by the local school orchestra, words of introduction by well-known school or other leaders, a showing of the talking movie, "Bobby Goes to School," a panel discussion, and brief concluding ceremonies.

The panel discussions were outstanding in their timeliness and enthusiastic reception. Each panel consisted of a chairman and four associate pediatricians, and in some cases an educator and a nurse. Discussors sat about the table and used microphones in the school auditorium.

Each chairman was equipped with questions received from parents or teachers in advance or preselected as suggestive questions by panel members after the panel was started, questions were invited from the floor on child health and school health problems. In many instances the questions were numerous and appropriate. Where they were specific the discussor tried to apply a generally helpful answer.

These meetings were timely because they came at an early period in the school year when parents and teachers have to face a winter of possible infections and health is an important consideration. Panel discussions at this time, of course, have been of interest to special scientific groups but this is one of the early

adaptations to this type of school health meetings. The discussors, that is, the panel chairmen and associates, were carefully selected, mostly from the ranks of Academy members in the Philadelphia area.

There were eleven meetings in eleven schools and the attendance at these meetings was as follows: 175, 550, 500, 525, 500, 175, 125, 800, 1000, 250, 400. This makes a total of 5,000, consisting mostly of parents, teachers, doctors, social workers, and nurses that attended these "Going to School Health Meetings." The acceptance was astonishingly good. Audiences were very enthusiastic about the meetings. Many claimed that they learned considerable. Among those who learned most probably were the chairmen and panel members. Discussion is at the present time going on relative to follow-up work to rivet the value of these meetings.

Dr. L. R. Brigman of Reno, Nev., has been elected vice-president of the Nevada State Medical Society.